SYNTHETIC BIOLOGY FOUNDRY VISION

VISION

The Synthetic Biology Foundry will unite the capabilities of the national laboratories to develop a robust, agile biomanufacturing platform accessible to researchers across the private and public sectors.

MISSION

The Synthetic Biology Foundry will integrate industrially-relevant production microbes, advanced tools for biological engineering, and robust processes for integrated biomanufacturing.

GOAL

The Synthetic Biology Foundry seeks to develop innovative, open-source, and scalable technologies that will enable a robust bioeconomy by reducing the time and cost of developing bioproducts.

THE NEED FOR A PUBLIC EFFORT

For forty years, researchers have been able to conveniently and precisely manipulate the genome of an organism to create products of interest. In the private sector, many companies have used genetic engineering and synthetic biology technologies to create new bio-based fuels and chemicals that can displace petroleum counterparts, while others have commercialized the those underlying technologies. Many of these efforts have been focused on specialization, where a company develops expertise and capabilities for a select host organism and a relatively limited set of products from that host. Due to the competitive nature of the field, much of this knowledge is not transferred outside of the company and other efforts repeat prior work. Improvements in technology, especially computing and laboratory automation, have meant that some of the work to build a strain is quick and relatively easy to accomplish. Despite this, there are still bottlenecks to achieving a robust process that can be implemented at the needed scale for production. Some of the biggest challenges remain around learning from experiments and processes and applying that knowledge to future work to design strains. While some companies are beginning to enter this space, the technology to do this is still in its infancy and is not expected to be widely available for some time.

The national labs have unique and complementary capabilities that can be united to build out a robust biomanufacturing platform that addresses the needs of companies in the bio-based fuels and products sector (and biomanufacturing more broadly). These capabilities include: biological discovery and application of new genes, proteins, pathways, and organisms, facilities for characterization of organisms' genomes, proteomes, and metabolomes for holistic understanding, high-performance computing, and facilities and equipment for integrating bioprocesses and scaling them up. These capabilities and facilities do not exist in the private sector. Additionally, the underlying research and

development, capabilities and facilities lie outside the core missions of companies. To truly turn biological engineering into biomanufacturing, the expertise and capabilities of the national labs must be united and informed by real-world challenges facing private industry.

KEY STAKEHOLDERS

The Synthetic Biology Foundry considers its stakeholders to include:

- Companies that develop bio-based fuels and chemicals
- Companies that develop instrumentation, equipment, software, and reagents for biological engineering
- Researchers at companies, national laboratories and universities that would like to build new strains
- Researchers at companies, national laboratories and universities that develop new bioproducts
- Researchers at companies, national laboratories and universities that develop new technologies
- Federal agency staff that support bioeconomy programs
- General public interested in a more economically- and environmentally sustainable bioeconomy

FRAMEWORK FOR THE SYNTHETIC BIOLOGY FOUNDRY

To achieve its mission, the Synthetic Biology Foundry (SBF) will unite the capabilities of the Department of Energy National Laboratories to integrate sophisticated synthetic biology tools including software for biological design, machine learning, high-throughput analytics, techno-economic and life cycle analyses, and expertise, into an agile and dynamic platform for biomanufacturing of microbes for production of bio-based fuels and chemicals. The SBF will focus its efforts on integrating the Design-Build-Test-Learn (DBTL) cycle of biological design while incorporating analysis that guides product/organism fit and selection, techno-economic and life cycle analyses, and process considerations for predictable scaling and process robustness. Figure 1 describes the proposed research and development focus for the SBF. As envisioned, the labs will use the techno-economic and life cycle analyses to develop a set of exemplar molecules, with industry and other stakeholder involvement, that address key barriers for the DBTL cycle and process integration to demonstrate an integrated biomanufacturing platform. These exemplar molecules will allow the SBF to benchmark and measure progress as the platform is integrated and optimized.

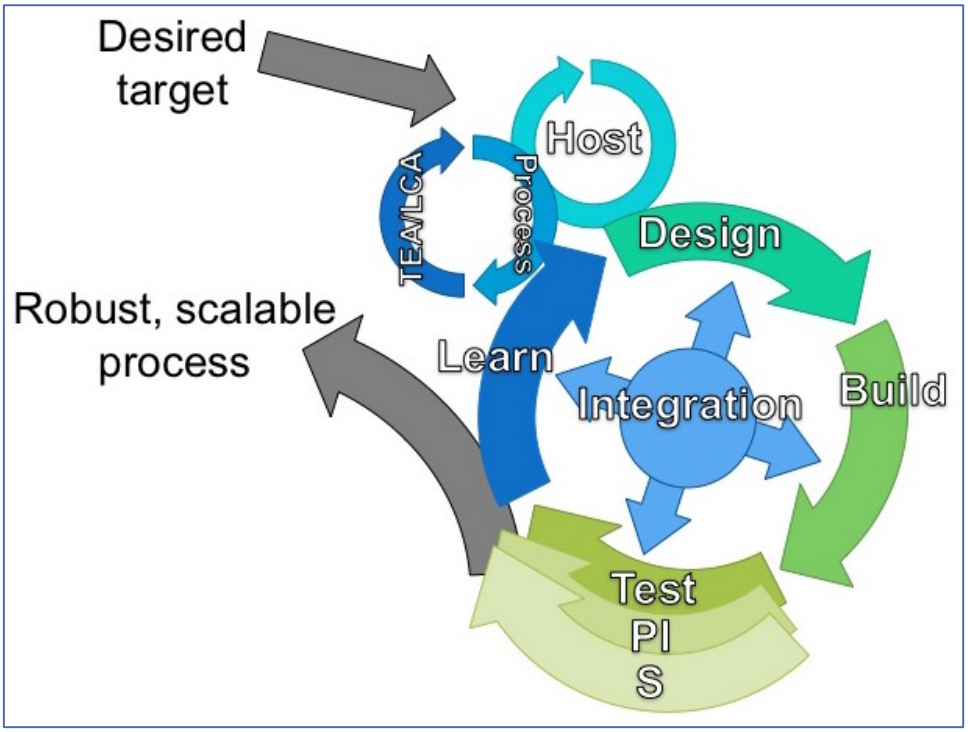

Figure 1. *The platform that the SBF will develop to deliver robust and scalable processes for desired target molecules. The core of the SBF effort will be to develop the integrated Design-Build-Test-Learn cycle, where Design is informed by techno-economic analyses, life cycle assessments, and process considerations that allow for optimum host organism selection. Test is represented by multiple arrows to indicate various dimensions of test, including bench-scale analysis (Test), integrated bioprocesses (PI), and scaling to relevant scales (S) for the bioprocess. Each of these dimensions of Test will provide valuable information for Learn and will be incorporated into the upfront TEA/LCA and process considerations for future rounds of Design.*

IMPACT AND THREE-YEAR ACHIEVEMENTS

The SBF will broadly enable biomanufacturing across the bioeconomy through the development of new host organisms an integrated Design-Build-Test-Learn cycle that is accessible to industry and to university and national lab researchers. The SBF is envisioned to enable companies to bring new products to market more cost-effectively and efficiently through the reduction of bioprocess design cycle times. With these improvements the SBF, in partnership with academia and industry, aims to:

- Decrease the energy intensity of current manufacturing processes by 40% over status quo
- Decrease the carbon intensity of current manufacturing processes by 60% over status quo
- Reduce time to market cycle time by 50% over status quo
- Increase biomanufacturing cycle efficiency (cost, time) >40% over status quo
- Develop new manufacturing technologies, increase US industry competitiveness, and create new opportunities for private sector growth

Progress and success for each target will be measured against an initial project baseline, then measured annually against that baseline. Some metrics that will be considered are: DBTL cycle time to industrially-relevant titers, rates, and yields; number of cycle iterations needed to reach those relevant

titers, rates, and yields; projected reductions in cost and environmental impacts for a target; and the number of person hours needed to achieve targets.

At the end of the initial three years of funding, the SBF will:

- Demonstrate an integrated Foundry platform, as measured by markedly increased titers, rates, and yields for production of 3-5 exemplar molecules over the initial baselines with reduced person-hour contributions to the DBTL cycle
- A public set of tools and technologies for rapid and facile engineering of biological organisms
- Publicly-available databases and software to improve biological design with an advanced starting point for production of targets over the current state of the art
- Genetically-tractable, industrially-relevant host organisms for bio-based fuel and chemical production
- Partner with industry and other collaborators to develop pathways for products of interest in relevant host organisms (initial partnerships to begin in year 2, fully integrated development by the completion of year 3)

Within five years, the SBF will be able to develop more than 100 concurrent targets in their corresponding host organism, with a cycle time of less than three months. At year 5, the targets will include some retrosynthetic pathways (i.e. targets for which no existing pathway has been identified) and some targets of opportunity (i.e. beachhead molecules that have the potential for further transformation into more than 30 end products). By year 10, we envision that most SBF targets will be designed through biological retrosynthesis and that the SBF will have a full complement of targets of opportunity in multiple host organisms. Table 1 outlines some target performance metrics for the first five years of the SBF.

	FY17	FY18	FY19	5 years
Number of SBF hosts in operation	5	7	10	>20
Number of concurrent target/host combinations per year	5	15	30	>100
DBTL cycle time	9 months	8 months	6 months	<3 months
Strain samples analyzed per year	35,000	50,000	75,000	>100,000

Table 1: *Cycle time and capacity targets for the SBF*

ELEMENTS OF THE SBF CORE R&D MISSION

DESIGN-BUILD-TEST-LEARN CYCLE

Design is the ability to design bioprocesses for desired target, including the necessary workflows to build out pathways in a host organism and the needed testing to understand performance. R&D for design includes the development of computer assisted design software for biological pathways, databases of known expression systems and the genetic tools available to build organisms. Design is further informed by iterations of techno-economic analyses and life cycle assessments combined with overall process consideration that allow for ideal host organism selection.

Build encompasses the organismal chassis for the designed pathways, liquid handling and other automated methods of assembling the genetic systems for the pathways, and transformation capabilities to insert pathways into the organismal chassis.

Test includes the assays, instrumentation, and equipment necessary to understand how a designed pathway behaves in a host organism. While test is often thought of as assaying the performance of an organism under specific growth conditions, the SBF will incorporate process integration and scaling into Test. Just as it is important to understand how a pathway performs in its host, it is also important to understand how that designed organism fits into an integrated process, including the feedstocks used and upstream and downstream unit operations. Additionally, understanding the performance at increasing scales is critical to understanding an organism's performance in the environments of fermenters or other reactors.

Learn is the linchpin to the activities of the SBF. One of the critical barriers still unaddressed in biological engineering is the ability to completely rationally improve upon design based upon data gathered in Test. Through machine learning, sophisticated statistical modeling, and metabolic flux analysis, this data will be translated into predictions that can be combined with TEA and LCA, process considerations, and host organism parameters to improve and predict the Design of future pathways and processes. As currently envisioned, the databases and information created through Learn will be made accessible to the community to share the knowledge gained and advance biomanufacturing broadly.

NEEDED CAPABILITIES TO IMPROVE DBTL FOR INDUSTRIAL PROCESSES

Techno-economic analyses (TEA) and life cycle assessments (LCA) enable researchers to understand impacts beyond the organism on process considerations. These analyses define criteria around pathway and host organism selection that allow for improved economic feasibility and minimized environmental impacts for a bioprocess and help direct research towards elements of a process that most influence cost or environmental performance.

Process considerations are key to design a robust bioprocess. The selected process includes many points where understanding the host organism and designed pathway are critical. Unit operations such as fermentation conditions and separations technologies are determined understanding how a particular pathway will behave in a selected host. Design can take potential contaminants, toxic byproducts, or any other number of factors into consideration to reduce the challenges inherent in integrating a process.

Host organism selection is a key step in designing a bioprocess. Beyond impacting key production metrics like titer, rate, and yield, organism selection also affects pathway and process design. Organisms that perform well at high-temperature can offer savings on the energy required to maintain low temperatures in fermenters. Organisms that perform well at low or high pHs can tolerate production of specific molecules. While there are well-developed industrial host organisms, there is still a great need for further development, including genetic manipulation systems and growth conditions, of a range of host organisms that can act as chassis for a variety of diverse bioprocess pathways. The host selection for the SBF will focus on covering a range of product spaces through a diverse slate of organisms that have the potential for wide use in industry (or are already widely used but can use improvement).

Process integration and scaling are critical for understanding strain performance in context of an overall bioprocess and its potential translation to an industrial setting. During process integration, the strain is grown at the appropriate scale using the relevant feedstock that has been formatted for the bioprocess and subjected to the appropriate pretreatment and saccharification process steps. Additionally, the downstream processing steps including product separation, purification, and upgrading are incorporated to understand and identify problems, as well as to provide data for analysis activities.

Integration of these activities is key to the mission, goal, and success of the SBF. Currently, Design, Build, and Test are implemented and integrated at varying levels in industry depending upon the mission, business model, and resources of a company. Learn still remains a critical barrier, with only a few companies investing in technologies to use machine learning or statistical methods to predict better organism and pathway design. A truly integrated DBTL platform that incorporates an understanding of overall process design, TEA/LCA, and scaling does not yet exist in private industry. The SBF will leverage and unite capabilities to offer an integrated platform that is accessible to companies and to researchers at the national labs for rapid and efficient engineering of biology.

R&D FOCUS OF THE SBF

The SBF platform will need to address the critical barriers that industry faces in order to develop a user base. To understand what these barriers are, as well as what and when they should be addressed by R&D within the SBF, the national labs involved in the consortium hosted an Industry Listening Workshop on March 15, 2016 in Berkeley, CA. Here we outline the R&D that the SBF will undertake, some of which was identified at the workshop. The full report from that workshop can be found in Appendix A. The R&D highlighted in the section will primarily be developed such that it can be integrated into the SBF platform. Whenever possible, the SBF will draw upon existing technologies and capabilities within the national labs.

DESIGN TECHNOLOGIES

Design begins with target selection, a process that, beyond chemical and biological expertise, includes market, techno-economic (TEA), and life-cycle analysis (LCA) as a means of developing a robust and prioritized list of molecular targets for the SBF to pursue. Since underlying datasets change over time, closely integrating and refreshing market analysis, TEA, and LCA together with bioprocess design is necessary. In collaboration with Integrated Analysis, Process Integration/Scaling, and the Industry Partnership Team, Design will demonstrate a design toolchain software architecture that enables push notifications (as proposed in the National Academy's Industrialization of Biology Roadmap), alerting the SBF as well as industrial partners when a bioprocess becomes viable. Many bioprocesses could achieve the same target. Beyond upstream (e.g., feedstock characteristics) and downstream (e.g., purification) possibilities, there are multiple conversion systems to consider, including different hosts, pathways, expression configurations, and bioreactor conditions. Design will demonstrate a design toolchain software architecture that enables end-to-end bioprocess design (as proposed in the Industrialization of Biology Roadmap), to anticipate and exclude subcomponent designs that diminish overall bioprocess performance.

The proposed Design tasks will leverage and integrate unique and existing capabilities and software tools (including SMRC (Species Manipulation Relation Cultivation – Host Onboarding), ICE (Inventory of Composable Elements – Design/Build), DIVA (Design Integration Validation Automation – Design/Build), j5 (DNA assembly design automation – Design/Build), SPL (Sequence Polishing Library

– Design/Build), SynTrack (Build workflow tracking), EDD (Experiment Data Depot – Test/Learn), and ArrowLand (multi-omics/flux visualization – Test/Learn/Design)), to build the design toolchain software architecture. A large portion of each Design task will continue to require hands-on contributions from domain experts until their knowledge is systematically codified into design software in later years. In collaboration with Learn, Design will support Build and Test by prioritizing designs that facilitate, maximize success rates, and minimizing the time and cost requirements of build and test procedures.

BUILD TECHNOLOGIES

Build will translate Design into biological reality, including DNA construction, the introduction of DNA into the host, and forward genetic screens to further modify target pathways and host metabolism toward higher titer, rate, and yield. Build will obtain information pertaining to host transformation and cultivation, developed by Host On-boarding and housed in the SMRC database, and use this information to engineer the selected host. Build tasks will include both genome modification of the host organism and introduction of the target bioproduct biosynthetic pathway. DNA construction will rely on Design to determine the optimal DNA construction strategy. Correctly assembled DNA constructs will be used for host engineering.

Build will use information provided by Design and Host Onboarding to develop, optimize, and implement standardize workflows for transformation and screening. Protocols for transformation and integration will be standardized across strains using landing pad technologies. Build will use the Integration systems scheduler to coordinate Build material exchange with Design and Test as well as coordinate builds that require sequential modification, i.e. genome modifications required before the target pathway can be introduced into the host. Build will coordinate with Test to supply strains and biomass for analysis. Since Build will inherently have established the capabilities for small scale cultivation, it will produce and supply material for initial Test validation of target molecule production, transcriptomic, proteomic and metabolomic analysis. Once Test has validated the production of the target, Build can further modify the host genome and bioproduct pathway via forward genetic screens, developed by the Host Onboarding Team.

TEST TECHNOLOGIES

Test will assess the performance of newly built organisms to identify specific improvements that can be made in subsequent DBTL cycles, as well as provide data for TEA and LCA. Culturing options will be guided by maximum throughput and minimum sample size consistent with the need of subsequent analyses (e.g., BioLector platform) to potentially larger scale for second or third iterations of specific Crop testing. Test will conduct transcriptomic, proteomic and metabolomic analysis, applied in concert or individually, depending on the data needs of Learn. Transcriptomics will be used to quantitatively assess gene expression across stages (time points) of a bioprocess or between different conditions. Proteomics will quantify target pathway enzymes, and identify post-translational modifications. Metabolomics based on LC-MS, GC-MS, MALDI, NIMS and NMR techniques will be used to identify carbon flux bottlenecks. The majority of these capabilities are already in place and running at the partner labs. In addition to multi-omic analysis, a number of specific assays for metabolites and specific enzymatic activities will be used *in vitro* or *in situ* for strain screening and selection. These assays will be based on different types of detection, sample volumes, and throughput.

Imaging capabilities will complement omics analyses and targeted assays. A vast array of light, spectroscopic imaging and particle based imaging capabilities are available at the national labs and provide the ability to examine organisms cultivated over a range of scales and different conditions. For some pathways, targeting enzymes to the proper cell compartment is crucial and imaging enables the

assessment of expression and localization of enzymes. Imaging is also valuable for examining critical cell morphologies, and for detection and examination of contaminant organisms in bioprocesses. These imaging techniques are to be used only as needed for troubleshooting targeting or morphology issues.

LEARN TECHNOLOGIES

Learn will leverage Test phenotypic data to direct Design towards increased product titer, rate, and yield. This process will be carried out through statistical and/or mechanistic modeling, as determined by effectivity vs. time requirements (e.g., mechanistic modeling takes longer but may be required when statistical methods plateau). The Experiment Data Depot (EDD) will store and provide standardized data that can be fed into a variety of algorithms and improve current models. Statistical modeling will focus on pathway improvement by using machine learning algorithms applied to multi-omic Test data. Scikit-learn package algorithms) will be used to predict production. We will then use these models to predict protein expression profiles that would increase production and work with biological part information to instantiate these optimal proteomics profiles. Mechanistic modeling will focus on intracellular flux analysis and pathway kinetic modeling. Flux analysis will elucidate carbon redistribution in the full host metabolism and identify bottlenecks that are dependent on the host, rather than the pathway. We will use ^{13}C labeling experiments to obtain accurate flux profiles and constrain genome-scale models. We will use these accurate profiles with COBRA algorithms to inform which host reactions are limiting production. Given the nascent nature of methods for predicting biological behavior, a significant fraction of Learn will be spent in leveraging Test data to improve current models. The large amounts of multi-omics data generated for the statistical approach will be used to parameterize ensemble kinetic models and provide part characterization for Design. In parallel, we will use the prior knowledge in the mechanistic models to constrain the feasible space for statistical models.

DBTL INTEGRATION

Integration will leverage and enhance INL's Bioenergy Feedstock Library capabilities to manage and track the logistics of samples shipped between the distributed components of the SBF via global unique identifiers (GUID) and resulting QR (quick response) barcodes. The logistical database will interconnect with other SBF databases including Inventory of Composable Elements (ICE) and the Experimental Data Depot (EDD) via RESTful API interfaces (with appropriate access controls) to connect samples with metadata. This integrated logistical sample management repository will enable distributed SBF operations to scale. To optimize the overall performance of the SBF, resource allocation (bandwidth and temporal ordering) must be under tight control. At the scale of the proposed distributed SBF, an automated solution to dynamic resource allocation is required. Integration will develop a systems-level model of the SBF (e.g., human and instrumentation resource bandwidth and time requirements for each component/operation). Integration will then develop a systems scheduler to automate resource allocation, and thereafter optimize the scheduler to continually improve overall SBF performance. These performance metrics will be tracked and published as monthly dashboards to the SBF team in order to validate progress, identify bottlenecks, and resource needs relative to productivity.

INTEGRATED ANALYSIS

The SBF will apply an integrated analysis approach coupling market, economic, sustainability and feedstock metrics to evaluate potential target bioproducts and beachhead precursor molecules. Given the broad range of products under evaluation in the SBF effort, market analysis will be pursued to understand the commercial prospects and potential supply chains for the proposed products. This analysis will be critical for proposed beachhead molecules to examine the variety of markets that these platform chemicals could enter. To evaluate the potential impacts of these products, the team will utilize

a range of resources for the market analysis including private consultant reports and trade magazines, as well as engaging stakeholders for guidance and reviews of any evaluations and assumptions. TEA will be utilized to identify process metrics and R&D needs for the development of economically viable production pathways for each molecule and will provide key data to support the LCA. These LCA analyses will consider GHG implications for the proposed molecules, as well as explore other sustainability drivers for production of these bio-derived products. Both TEAs and LCAs will be developed using consistent methodologies with other DOE-supported evaluations to ensure the analysis results are comparable and transparent. The Analysis team will work closely with the researchers to provide information needed for the integrated DBTL approach.

HOST ONBOARDING

New, industrially relevant hosts are needed to expand the economical production of target molecules. The Host Onboarding team will leverage National Lab expertise in microbiology, molecular and cellular biology, genomics, bioinformatics, metabolic and biochemical engineering, TEA, LCA, multi-omics, and process design to identify new production hosts that have desirable traits and could have a large economic impact on target production and separations. We will also solicit input from industry and academia to identify promising hosts. Examples include organisms that naturally have substantial metabolic flux through critical metabolic pathways, that thrive in conditions that allow new processing conditions (e.g., extreme pH, salinity, temperature), that allow feedstock flexibility including the ability to co-utilize multiple carbon sources (e.g. sugars and lignin) simultaneously, that have diverse oxygen requirements, or that possess other novel and useful traits. Because diverse target molecules and varied processing schemes will require organisms with diverse properties, one of the goals of the Host Onboarding activity will be to cover as much of the relevant biomanufacturing space as possible with a broad pool of host traits.

In order to be fully on-boarded into the DBTL pipeline, a certain level of basic tools and knowledge will be required to facilitate the cycle, and the on-boarding process will involve meeting these criteria. The general host onboarding process for the first three years of the SBF is describe in Figure 2. For each organism, molecular tools will be required, including a sequenced genome, DNA transformation methods, selectable and counter-selectable markers, deletion/overexpression/heterologous expression tools, and high throughput tools for genetic manipulation. The ability to characterize metabolic flux will also be critical, including a complete carbon and electron balance, a metabolic model construction, and ^{13}C fluxomics. This experimental work will primarily be performed within the DBTL task, with the exception of genetic tool development. The above criteria will be organized into tiers, which will describe minimal criteria to be met for onboarding (Tier 1), as well as additional levels (Tiers 2-4) that can be met over time for more advanced use of these hosts in DBTL. Furthermore, all of the information relevant to the onboarding process, including culture conditions, protocols and standard operating procedures, and data collected, will be stored in the SMRC and related accessible databases that are tightly integrated with other SBF software tools and with other tasks.

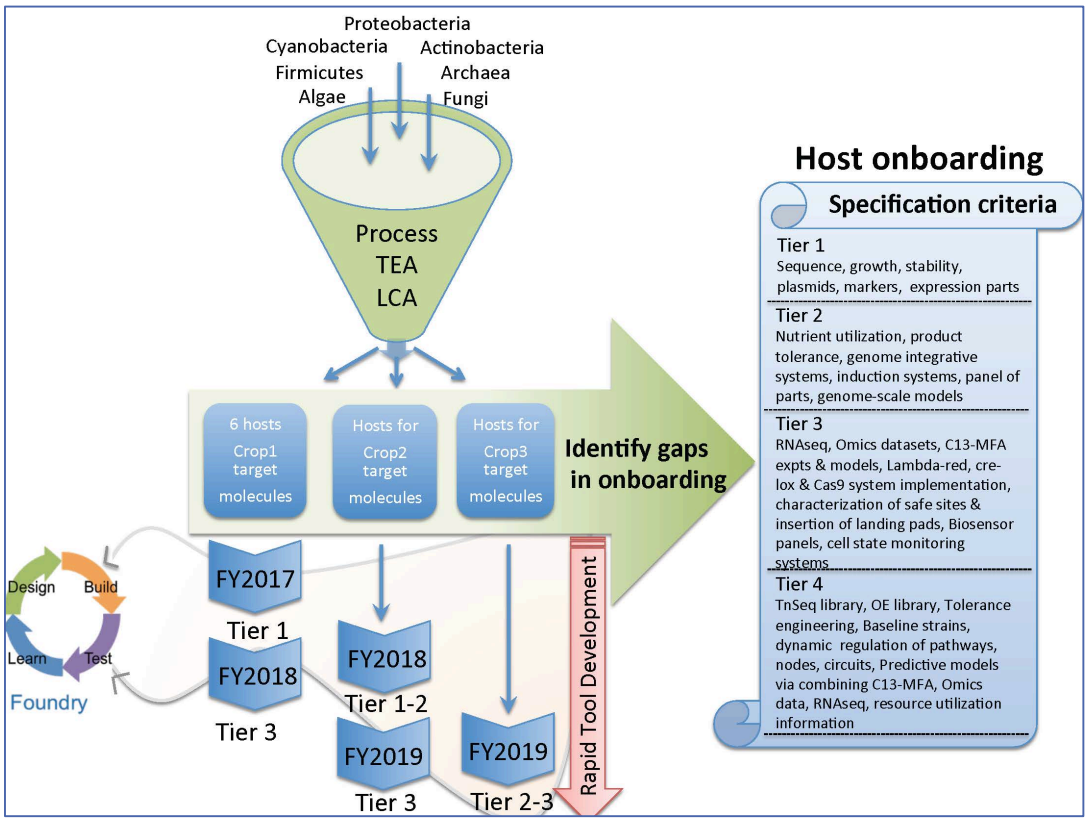

Figure 2. *The host onboarding process.*

PROCESS INTEGRATION AND SCALING

A primary output of the DBTL cycle, as well as a major component of Design and Test components of DBTL, involves process integration and scaling for the selected target molecules in the proposed SBF effort. This includes a focus on several key aspects including:

- The standardization, production, shipping, and storage of hydrolysates to be tested in DBTL
- The comparison of clean sugar processes with hydrolysates
- Fermentation testing and scaling (coupled to Test) to improve titer, rate, and yield
- Process integration (coupled to Design and Integrated Analysis) to provide integrated, bench-scale data for TEA and LCA
- Scaling of fermentation where necessary to produce data for the Learn component of the DBTL cycle

For a feedstock, the SBF will use corn stover. Currently funded efforts in feedstock handling and pre-processing will be leveraged to provide uniform corn stover compositions for reliable, repeatable biomass deconstruction. Advances from other DOE-funded efforts will be leveraged for improved feedstock properties as developed. Hydrolysate can be produced and shipped to SBF partners in 1-100 L quantities as needed for the Test component of DBTL. In addition, a major component of the Host Onboarding process will rely on initial screening of candidate hosts with this biomass-derived hydrolysate.

Fermentation testing will be conducted as needed in the SBF when titer, rate, and yield measurements need to move beyond results obtainable in shake flask testing experiments. Most fermentation testing will be done at either small scale (e.g., in µ-scale multiplexed bioreactors) up to the 0.5 L scale (e.g., at LBNL's ABPDU or NREL's IBRF). Fermentation optimization will be conducted on promising strains identified in shake flask trials, and when titer, rate, and yield improvements can be gained by moving to controlled bioreactors. These fermentation results will be crucial for both the Test and Learn components of the DBTL cycle, and 'omics measurements will be employed for bioreactor tests as well to identify metabolic bottlenecks and to inform Learn. Similar to typical efforts in bioprocess development, titer, rate, and yield in fermentation testing will be the primary objective. Scaling will occur beyond 0.5 L (up to 300 L) where needed for harvesting larger biomass samples (e.g., for transcriptomics experiments) and in cases where the Learn component of the DBTL cycle would benefit from scaling up (or down) for predictive scaling purposes, when titer, rate, and yield targets are reached at smaller scale, or when larger-scale production of a target molecule is needed for demonstration purposes.

LABS

The SBF platform will continuously incorporate new technologies that are ready to be onboarded. In order to do this, there will be a staging ground known as the Labs. This is where new technologies will be tested in the context of the platform before being integrated into workflows. This will allow the SBF to ensure that the technologies are properly vetted without diverting resources from normal operations.

STANDING UP THE SBF

To unite the capabilities of the national labs into the SBF, it is likely that the U.S. Department of Energy's Bioenergy Technologies Office will fund an effort to unite the national lab's capabilities in this space. The goal of these activities is to assemble and demonstrate a functional DBTL cycle for multiple targets and organisms. In the first year, we propose to work with no more than 5 unique organisms and related pathways for the production of at least 5 unique molecular targets. We have identified two organisms, *Streptomyces venzuelae* and *Pseudomonas putida,* to serve as the foundational SBF platforms. Up to three other organisms will be identified by the SBF team, based on genomic maturity and tools, in the first three months of the project. For this effort, molecules will be grouped for staging through the Foundry, by risk, metabolic pathways, and market analysis. Initial groups will focus on low-risk targets that can be used to build the integrated SBF infrastructure, while later groups will focus on high-impact targets to enable industry. The later groups may include "targets of opportunity," beachhead molecules that allow for many further transformations via biological and chemical upgrading to maximize the potential market opportunities for the targets to enable industry. After the initial 18 months of the project, the SBF platform will be fully integrated and will be able to engage in industry collaborations to develop targets of interest. Industry collaborations before this period will be focused on instrumentation or on development of host organisms to develop technologies needed for an integrated DBTL platform.

MANAGEMENT OF THE SBF

The SBF will be a distributed consortium of national labs. While some elements may be co-located for convenience (e.g., Build technologies that work most efficiently when sited together), others may be geographically dispersed to leverage existing capabilities, facilities, and capital investments.

The SBF aims to have a significant industry-facing component that will perform collaborative research with interested partners. The SBF will operate in a similar fashion to other EERE-industry collaborative efforts, such as the Advanced Biofuels Process Demonstration Unit, the Integrated Biorefinery Research Facility, and others. The SBF will not be a formal User Facility as defined by DOE.

MANAGEMENT STRUCTURE

The SBF will have an Executive Committee composed of members representing each of the partner national labs. The Executive Committee will be responsible for the overall strategy of the SBF, oversee the Project Management and Integration team and the Industry Partnerships team, and work with the Industry Advisory Board to ensure that the SBF is continually addressing challenges faced by industry.

Day-to-day operations of the SBF will be the responsibility of the Project Management and Integration team. This team will be responsible for managing the activities of the various technical teams, as well as ensuring that technical teams are working together. This team will also be responsible for developing the integration of individual technologies. Finally, this team will manage the scheduling of projects through the SBF to ensure that resources and time are allocated appropriately, new technologies are continually evaluated and onboarded, and potential workflow impedances are understood, mitigated, and managed.

The technical teams (Targets, Hosts, Design, Build, Test, Learn, and Labs) will be performing the work of the SBF. The Targets team will evaluate exemplar molecules for the SBF and provide TEA, LCA, and process considerations for design. The Hosts team will evaluate host organisms for use at the SBF, define the needed requirements for onboarding, and fill in gaps in those requirements. The Design, Build, Test, and Learn teams will be the technical experts in their associated technologies and executing the R&D for SBF projects. The Labs team will be continually testing new and emerging technologies to ensure that they can be onboarded into the platform without impeding the normal operations of the SBF.

The Industry Partnerships team will be responsible for developing relationships with industry partners, developing scopes of work with the industry partners and the Project Management and Integration team, and handling the intellectual property agreements between the SBF and its industry partners. This team will report to the Executive Committee and will work closely with the Project Management and Integration team to ensure effective partnerships with companies. To facilitate interactions with industry, the SBF will have a single point of contact, or concierge, to manage interactions between the labs' intellectual property offices. The SBF will also maintain a public website that contains information about working with the SBF, along with recent publications, patents, and other disclosures of of work, to aid in dissemination of SBF R&D products to interested stakeholders.

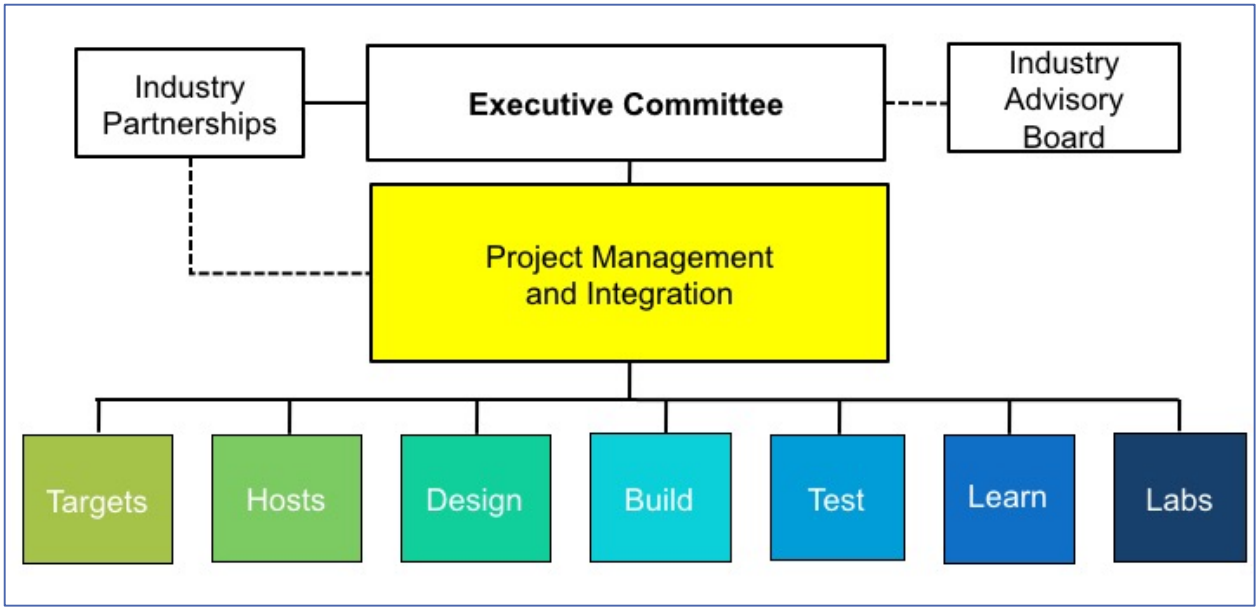

Figure 3. *Proposed management structure for the SBF.*

INDUSTRY ADVISORY BOARD

To ensure that the SBF addresses the needs of companies in the bio-based fuels and chemicals industry, an Industry Advisory Board (IAB) will be established. The IAB will work closely with the Executive Committee to establish strategic goals for the SBF. The IAB will also ensure that the SBF is addressing the critical barriers to rapid, cost-effective, and efficient biological engineering for industrial processes to remain relevant to its industry stakeholders. The IAB could also provide strategic direction for potential opportunities offered through the SBF, such as voucher programs, that allow for companies to compete for sponsored projects through the SBF.

INTELLECTUAL PROPERTY AND WORKING WITH INDUSTRY

INTELLECTUAL PROPERTY PRINCIPLES

Whenever possible, the SBF intends for intellectual property (IP) generated by the national lab partners or with public funds to be accessible to the larger community. The national labs will work together to establish a portfolio of background IP that can be brought to bear in standing up the SBF. The labs will establish a streamlined process for managing IP developed under the SBF. The SBF Industry Partnerships team will investigate models for accessible IP and develop methods of licensing SBF IP to ensure that it is minimally encumbered for use by industry. In general, the SBF will protect IP it generates through non-exclusive licenses to maintain accessibility for the broadest spectrum of stakeholders. For specific interactions with companies, the IP will follow the process of inventorship outlined in the specific agreement.

The preferred IP management model for industry is a single point of contact and a streamlined set of agreements for partnering with the SBF. The Industry Partnerships team will lead up the IP management activities. To facilitate single point-of-contact IP management, the SBF will reserve some funds for IP management. The SBF will use these funds for patent prosecution and IP licensing. In this model, the Executive Committee, in consultation with the Industry Partnerships team, will decide which

IP will be patented and licensed. The SBF will pay for 50% of the patent prosecution and the national lab(s) that own the IP will pay the other 50%. If the SBF declines to prosecute a patent, the national lab(s) that developed the IP will be able to prosecute if desired.

The SBF will have streamlined agreements for industry projects. Companies that wish to pursue Cooperative Research and Development Agreements (CRADAs) or Work for Others agreements (WFOs) will work with the Industry Partnerships team to develop statements of work for SBF projects that apply to all labs in the consortium. Additionally, Materials Transfer Agreements and Non-Disclosure Agreements will be standardized and apply to all labs in the SBF. It is expected that the first industry partners for the SBF will be focused on individual elements of technology development, including instrumentation, with an integrated platform available for specific target development ready for industry collaborations within two years of standing up the SBF. By the end of year three, the SBF will have the capacity pursue multiple industry-led targets.

At the Industry Listening Workshop, companies expressed interest in creative mechanisms for funding CRADA or WFO projects with the SBF. Besides standard cost-recovery models, the SBF will investigate a voucher program, similar to the Small Business Voucher program, with its EERE sponsors. A voucher program would allow companies to compete for EERE-sponsored projects with the SBF with minimal cost share. Industry members also expressed an interest in cooperative technology development activities with the SBF to develop new DBTL technologies. In this case, the Executive Committee would consult with the IAB to develop strategic opportunities in this space that could be funded by a voucher program or a competitive solicitation with the SBF's EERE sponsors.

Companies may also be interested in testing or learning about the SBF platform prior to licensing and bringing technologies in house. To facilitate that, the SBF could host visiting researchers from private industry. In these cases, the companies would receive a non-exclusive license to the platform technologies after a specified duration of training.

DATA MANAGEMENT

One of the first management tasks for the SBF will be to define a data management plan. While this plan will require negotiation between the labs' intellectual property offices, some general principles can be identified. Data resulting from publicly-funded R&D at the SBF will be made accessible to stakeholders as much as possible through standardized databases and software. The data will be quality controlled to ensure accuracy. Companies that work with the SBF will have the option to make their data available for improving Learn capabilities. Should a company choose not to share its data, any data and/or IP generated during a project will be firewalled from the public-facing data.

REPORTING

The SBF intends to be an open and accessible resource for the rapid, cost-effective biological engineering. To that end, the SBF will report regularly on its progress in a transparent manner. Regular reports will be made to EERE through the Annual Operating Plan process and its associated reporting structure of quarterly reports. Results from publicly funded projects will be published in scientific and technical journals, as well as highlighted on a public website. Available licensing opportunities will also be published on the website.

The Industrial Advisory Board will be convened on a quarterly basis. The Executive Committee and SBF staff will report out on progress, new strategic foci, and other business to the IAB. The IAB reports will be available to EERE following the meetings.

The SBF will convene an all-hands retreat on an annual basis to facilitate interactions between staff. EERE and IAB stakeholders will also be invited to attend the annual meeting. This will provide an opportunity for SBF leadership to update on progress, future directions, and highlight SBF successes. It will also serve as an opportunity for staff in the distributed consortium to meet and network, facilitating improvements in the integration of activities and identification of new R&D directions.

CONCLUSION

This document outlines a framework of operations for the Synthetic Biology Foundry of national labs, including the R&D foci for the SBF and a proposed management structure. This document is informed by discussions with industry stakeholders, EERE staff, and staff from the national labs. Further engagement with industry, other Federal government stakeholders, academic researchers, and the community will be sought out to improve the framework.

APPENDICES

Appendix A. Industry Listening Workshop report

Appendix B. Industry Listening Workshop agenda

Appendix C. Industry Listening Workshop ThinkTank report

INDUSTRY LISTENING WORKSHOP REPORT

INTRODUCTION

On March 15, 2016, the national labs involved in the Synthetic Biology Foundry held an Industry Listening Workshop to gather input from industry on how a public consortium of national labs could advanced current biomanufacturing processes. 67 participants attended the workshop; 37 participants represented 32 companies with interests in biomanufacturing and biological engineering. Participants were asked to provide input on R&D barriers that could be addressed by the SBF, as well as management of the SBF itself (see agenda, Appendix B). Breakout sessions were facilitated to gather specific input on topics of interest and participants could provide input verbally or through the ThinkTank tool (see ThinkTank report, Appendix C). Below is a summary of the breakout sessions and the overall concept.

MANAGEMENT AND INTELLECTUAL PROPERTY TRACK

CONSORTIUM MANAGEMENT

Several models of management were presented and were briefly discussed although most people seemed more interested in a more general discussion of the mission of the project. A structure with a Director, a Board of Directors, task leaders, and a Scientific Advisory board was discussed. There appeared to be little concern with the concepts of the Director, a Board of Directors, and task leaders. The Director would work with the task leaders on the day to day operations. The Director would work with the Board of Directors on major policy and monetary issues. The Board would likely be representative of the partners in the project and some outside directors. There was little discussion of a Scientific Advisory Board.

There was a strong consensus that leadership needs to define and communicate to the staff mission of the foundry and have staff aware of IP considerations when working with industry. Also, there should be real time transparent tracking of progress especially on dependent tasks. A live and interactive tool (e.g., a Gaant chart) was recommended. Rather, the one overwhelming consensus from the discussions of the management structure was the need for an involved industrial advisory board. The board would provide input to the management of the consortium on plans and directions in addition to reviewing progress but would not have a direct role in management. A nine-member board was recommended that would meet on a quarterly basis. If there is an annual meeting of the consortium the board would be invited and count that as one of the quarterly meetings. There was no discussion of the methodology for selecting the board but there was a consensus that the board membership be on a staggered rotating basis so that the whole board was not replaced at one time. The board could include representatives from a set of companies with diverse interests (e.g., production of biomolecules, utilization of

biomolecules, a range of company sizes) and could include venture capitalists. There was considerable concern about balancing the needs and representation of larger and smaller companies that may have different interests. For example, representatives of larger companies recommended a focus on common problems (e.g., contamination in fermentation, ways to capture volatile products, high throughput screening) where representatives of smaller companies wanted to see work on specific hosts and molecules (such as the "beachhead" molecules).

A non-disclosure agreement would be required of both the Industrial advisory board members and any outside directors on the Board of Directors. There is still a possibility of a separate scientific advisory board to advise on scientific directions and approaches.

INTELLECTUAL PROPERTY AND SPONSORED PROJECTS

A key theme that arose from industry participants regarding IP and data management was focused around balancing transparency with privacy, and combining this with an ease of contracting and communication. With respect to transparency, participants expressed a desire to see a single portal of information regarding Lab capabilities in general and also specifically focused around the Agile Biomanufacturing Consortium. A concern was raised that it's currently very difficult to identify researchers, facilities and programs at the Labs without a high degree of detailed knowledge to navigate the various websites, as an example. This theme propagated into feedback that they'd like a single portal to manage IP and contracting for the consortium, even if work may be happening in a somewhat distributed fashion. Industry participants also communicated that they would like to have the IP terms and contract types clearly articulated in a public, accessible way, alongside the description of Lab capabilities in a unified portal or website. In addition, having some level of core or commonly accessible IP around foundry infrastructure and engineering approaches was highlighted as important, so that individual industry stakeholders could replicate parts of the consortium independently. On the flip side, most participants also stated a clear need to own and protect specific inventions and IP focused on their own molecules, pathways and production processes that may be developed under CRADAs or WFO agreements with the consortium.

FUNDING OPTIONS FOR WORKING WITH THE CONSORTIUM

In this session, participants were asked to provide input on various funding mechanisms that would drive industry collaborations with the SBF. Participants were interested in competitive funding opportunities that would cover some costs of access and project sponsorship, either run through EERE or by the SBF. The group believed this would be an opportunity for an advisory board to play a role in determining the scope of the opportunity. When the participants were asked about companies paying a premium to "jump the line" of projects, they were uncomfortable with the concept. Many felt this would crowd out smaller companies without resources to pay to accelerate projects and result in the SBF being a *de facto* R&D arm for large, established companies. Participants felt some sort of sliding scale for access would be one mechanism for ensuring that small companies that may have a greater need for SBF capabilities would be able to get access. Finally, participants expressed an interest in having a "menu" of options for working with the SBF and clear insertion points. They believed that some a la carte options would be beneficial and drive industry engagement more than a one size fits all model.

MOLECULE SELECTION FOR THE CONSORTIUM: WHAT ARE GOOD PROOFS OF CONCEPT?

During the discussion on the molecule selection for the consortium, a range of potential types of products were reviewed by the group. Although specific types of molecules were proposed ranging from proteins to direct and functional chemical replacements, the group proposed that the best path forward for the consortium would be to focus on molecules that have the largest barriers and greatest challenges to overcome for microbial production. It was concluded that the greatest impact of the consortium could be realized if the consortium focused on overcoming these specific challenges, targeting transformations, and advancing the science to enable these technologies.

Specifically, breakthroughs that overcome the conversion barriers would help to support future technologies five to ten years down the road and would create the opportunity to produce a range of molecules including chemicals and biofuels. This type of translational R&D that allows products to come to market faster and at a lower cost would have the biggest impact on both DOE and the biomass conversion community. Further, the group encouraged the development of various tools that could accelerate the growth of both breakthroughs in R&D and in industry, including the development of assays to facilitate high-throughput screening and data integration approaches which could support the omics platform. Beyond focusing on a single type of molecule, the beach head concept was discussed which could result in the production of a range of products from biomass. These novel molecules could result in a broad spectrum of bio-derived products with unique properties not currently produced from fossil feedstocks. To fully understand these types of molecules and the industrial needs for these types of products, the group encouraged the consortium to pursue a strong engagement with the chemicals industry. The group also suggested that the specific pathways being pursued should consider the economics and the sustainability impacts (including greenhouse gas emissions, water usage, and toxicity) for a given product, as well as considerations that these products could have on growing the bio-industry and the US economy.

ADVISORY BOARD ROLES AND RESPONSIBILITIES

Attendees of the Advisory Board session of the Management and Intellectual Property track discussed a number of topics including the important functions of an advisory board, the establishment of a charter for an advisory board, logistics including size and meeting frequency, and the characteristics/experience of ideal board candidates. To begin, the attendees mentioned that an industrial advisory board would be a key component of the BioFoundry, allowing the Foundry to maintain industrial relevance and to work on new problems that had not already been addressed within industry. The functions of an advisory board that were discussed included helping identify the identity of priority or beach-head (or priority) molecules, providing feedback on the Foundry's technical progress and approach, and providing real-world guidance on market and policy factors. The board would also serve as a sounding board for BioFoundry leadership. Overall, the board could have the potential to help the national laboratories build equity in industry that they do not currently have. The types of people to be recruited for the board include those who are invested in the Foundry's success, those who have the ability to provide technical feedback from multiple disciplines (e.g., chemical engineering, biology), employees of non-governmental organizations, and academics in addition to experienced industry members.

Regarding structure, the members of this session thought nine was the advisable size of the industrial advisory board. They strongly suggested having a charter that clearly defined the role and responsibilities of the industrial advisory board including how their input would be used by Foundry leadership. The session attendees advised that the industrial advisory board should meet quarterly with at least two meetings/year in person. They also advised that the term of appointment to the board should be three years but rotation of members should be staggered to retain some institutional knowledge and avoid full board turnover.

R&D BARRIERS TRACK

DESIGN: BUILDING BETTER BIOLOGICAL PATHWAYS FOR PRODUCTS

Input around the Design component of the proposed SBF focused primarily on the most significant R&D and policy barriers. Industry representatives highlighted the need for on-boarding new, flexible hosts that are either somewhat thermophilic (to avoid bioreactor cooling costs) or, more ideally, hosts that match overall process conditions and the target molecule(s) to minimize processing and capital costs. The need for novel pathway and gene elucidation was heavily stressed as well, as "IP-free" enzymes are difficult to obtain towards desired targets and this si a major limiting factor in Design. This topic includes the need for rapid evolution of versatile enzymes (e.g., P450s) or the development of versatile, broad substrate-specificity screening kits to enable new biological chemistries, towards the aim to compete with purely chemical synthesis of target molecules. Regulatory aspects in terms of biosafety and deployment of genetically-modified hosts were raised throughout the discussion, especially in the context of algae or intracellular products, which led to a focus on secreted products that do not exhibit the same regulatory hurdles. The need for early, frequently updated techno-economic and life-cycle analysis was also highlighted as a key component of Design. There was general enthusiasm around "push" tools as a new component of the proposed SBF.

BUILD: PUTTING BETTER BIOLOGICAL PATHWAYS INTO NEW AND ESTABLISHED HOST ORGANISMS

A major theme in the “Build: Putting better biological pathways into new and established host organisms” was the need for new biological platform organisms beyond *Escherichia coli* and *Saccharomyces cerevisiae*. These new platforms should allow for operation conditions beyond the capabilities of *E. coli* and *S. cerevisiae*, such as having an extended productivity phase and operation at high temperature, low pH, in the absence of sterilization, or on complex substrates, resulting in specific TEA/LCA benefits over the state of the art. The major barriers to industry adopting new organisms include the lack of genetic tools such as transformation protocols, gene deletion systems, well characterized promoters; lack of fundamental knowledge about poorly characterized organisms (i.e., metabolic pathways, gene regulation, etc.); unknown phage resistance/sensitivity; unknown robustness; and unknown tolerance to products and intermediates. Further, desired new platforms should be able to produce multiple different target molecules. Aside from technical and scientific barriers, another major concern about new organisms was potential regulatory barriers, especially in the realm of food products. Rapidly overcoming these barriers was suggested to be an important target for the Synthetic Biology Foundry.

Little interest was expressed for the development of new DNA-building technologies or capabilities, though some expressed an interest in having a focus on the next generation of DNA synthesis technologies. There was discussion on the merits of moving to micro or nano scales for the Build and Test parts of the cycle, using microfluidics, wave technology, or other tools. However, some expressed concerns about the ability to screen and detect at the nanoscale. Overall, many industry representatives emphasized the desire for work to remain in the "innovation" area, rather than focusing on "operation" work such as scale-up.

TEST: ASSAYS AND TOOLS TO UNDERSTAND PERFORMANCE OF PATHWAYS IN HOSTS

A framework of existing capabilities and emerging needs driving the development and implementation of the TEST arc of the DBTL cycle was presented. Culturing capabilities spanning 7 orders of magnitude in volume (100µL to 1000L) are needed to facilitate high throughput analyses, obtaining high quality samples for downstream analysis by various 'omics capabilities, and development of scalable bioprocesses. The National Labs and User Facilities have a broad and deep array of tools in genomics, transcriptomics, proteomics and metabolomics to examine strains arising from the Design and Build portion of the cycle tested in various culturing environments. There is considerable room for technology development in some of these areas, e.g., faster quantitative metabolomics, proteomics of post-translational modifications, etc. Data analysis is an area requiring continuous development and improvement for all of these analytical techniques to cope with the explosion of data, the integration of meta-data from the experiments and winnowing out the relevant information from complex experiments. Other analytical techniques that are narrower rather than global (at the cellular scale), or even very specific are developing and have been implemented in particular areas. Sample handling technologies such as microfluidics will also be beneficial in developing high throughput, specific and sensitive analyses.

The industry represented at the workshop ran the range from very small start-ups to established mid-size and large biotechnology companies. Thus, needs and interests in different types of routine to developing technologies varied as well. A universal theme that emerged from the participants was an emphasis on the value of time in their environment. Building or extending capabilities in high throughput tools and rapid analytical techniques was a consistent theme in the discussion. Strain engineering runs the gamut from rational, to directed, to random mutagenesis and selection. Hence, tools and assays to screen large numbers of strains are required, e.g., some companies are screening up to 100,000 strain variants per month. Thus, there is a need for technologies that enable rapid development of sensitive and specific assays for various substrates and products that can be performed in seconds to minutes. Examples include small molecule detection technologies, like antibodies or aptamers, linked to a fluorescent reporter of high sensitivity, fidelity and accuracy. Accuracy and precision are important when assaying for small percentage increases in titers from an already highly productive system. Computational tools to analyze the deluge of 'omics data was another emphatic need. Development and employment of complex algorithms, techniques and software packages (e.g., machine learning) to find the important biologically relevant leads amidst the complex and voluminous data is a challenge that would be extremely beneficial if met! Discovering and understanding new pathways to various known or novel molecules is another need that falls naturally under the purview of Agile Biomanufacturing. Associated with this is the discovery and characterization of unknown and novel enzymes or entire classes of enzymes, as well as known classes of enzymes that are difficult to assign substrate and product specificities,

based on amino acid sequence similarities alone, e.g., cytochrome P450s, terpene synthases, polyketide synthases, transporters and glycosyl transferases. Increasing time efficiency and increasing the value of data were the two main themes of the day.

LEARN: MACHINE LEARNING AND STATISTICAL METHODS FOR IMPROVING DESIGN, BUILD, TEST, PROCESS INTEGRATION, AND SCALING

In this session, participants were asked to provide input on how data generated through SBF projects could be used to improve future pathway and process design. Some of the biggest barriers for industry that were noted by participants were the inability to link databases, incompatible data formats from different instruments and equipment, and lack of standardization between datasets. Participants thought that the SBF could address some of these concerns by pushing data into standardized formats and by assessing or ensuring the quality of the data that is fed to machine learning and statistical models. Currently, companies do not feel limited by computing power but few are pursuing “big data” approaches to biology. Participants expressed concern about how the SBF would protect business sensitive or confidential company data on projects at the SBF, but thought an opt-in option to share data would be acceptable for companies that wanted to feed their data into the Learn capability.

PROCESS INTEGRATION AND SCALING: BIOPROCESS DEVELOPMENT AND SCALING, INCLUDING FEEDSTOCKS CONSIDERATIONS

The discussion around Conversion and Process Integration focused on the need for broad-substrate specificity hosts that are able to tolerate lignocellulosic hydrolysates and rapidly co-utilize the sugars therein, which mirrors topics covered in the Build discussion. It was suggested that beachhead molecules be selected for scaling and integration that focus on the different process space, such as secreted phase-separable products or hydrophilic products, which would require different separation unit operations. It was stressed that if predictive scaling were possible from the SBF, this would be a good investment of funds and energy. Additionally in scaling and process integration, the issues of overcoming leaky metabolism, phage resistance, and overcoming issues with bioreactor contamination were raised, as all of these lead to huge cost burdens for the biorefinery. From a bioreactor operation standpoint, industry representatives brought up the need for more robust aerobic hosts and the need for new, readily available, cheap electron acceptors for anaerobic hosts.

Feedstock discussions centered on mitigating the impact of variability in feedstock attributes such as physical and compositional aspects that impact process integration and scale-up. It was discussed that for high value bioproducts intended to enable biofuel production at industrial scales, a biorefinery would necessarily need to utilize a variety of feedstocks, and thus consideration of the variability among those feedstocks will be important for increasing the speed of design, integration, and scale-up of efficient and cost effective processes. It was noted that compositional aspects and variability of feedstocks primarily impacts downstream separations and significant variability can lead to high costs for these separations. An additional impact of feedstock variability is that it limits the speed and success of scaling the process, and the costs/benefits of mitigating this variability need to be well understood early in the development phase to maximize success going forward. Beyond compositional differences and variabilities that impact organism development, physical differences and the presence of catalyst poisons (for hybrid processes) were noted as impacting scale-up and process integration. Technoeconomic analysis early in the development phase was noted as being

important to guide where in the process the issues would be cost effectively mitigated (i.e., prior to or during conversion).

THOUGHTS ON OVERALL CONCEPT

Before and after the breakout sessions, participants were asked for their thoughts on the overall concept. Many expressed a desire to see a framework for the SBF in order to provide more specific comments. The Vision Document is meant to provide that framework. Participants believed that the SBF would be a valuable resource to the bio-based fuels and chemicals industry, especially if it served as an accessible data and technology source. While there are some companies operating in a similar R&D space, participants believed there was space for a public consortium that would address barriers that pertain to all companies. There were concerns about intellectual property management, however there are many examples of national lab-industry partnerships that can be used as models for the SBF. Overall, participants believed that a publicly-funded biomanufacturing consortium would solve critical challenges to the benefit of the bioeconomy.

AGILE BIOMANUFACTURING

Industry Listening Workshop Agenda

March 15, 2016

General sessions

8:00 AM **Introduction to Agile Biomanufacturing and Workshop Overview**

8:00 AM Welcome and overview of the Agile Biomanufacturing concept
Jay Keasling, Lawrence Berkeley National Lab

8:15 AM Synthetic biology and biomanufacturing in the DOE Bioenergy Technologies Office
Kevin Craig, Department of Energy Bioenergy Technologies Office

8:30 AM Foundry vision and proof of concept
Nathan Hillson, Lawrence Berkeley National Lab

9:00 AM Process integration and predictable scale-up
Gregg Beckham, National Renewable Energy Lab

9:15 AM Overview of workshop and intended outcomes
Katy Christiansen, Lawrence Berkeley National Lab

9:25 AM Using ThinkTank
Jodi Grgich, Idaho National Lab

9:45 AM **Industry Input Session: Discussion of Agile Biomanufacturing Concept**

10:30 AM ***BREAK***

10:45 AM **Breakout sessions (see reverse)**

12:45 PM ***LUNCH***

1:45 PM **Breakout sessions**

3:45 PM ***BREAK***

4:00 PM **Breakout session**

5:00 PM **Reconvene in general session**
5:05 PM **Final input session and wrap-up**

Breakout Sessions

Breakout session format: Breakout sessions will be an hour long, consisting of 5-10 minutes of overview presented by the facilitator and followed by 50 minutes of guided discussion for stakeholders to provide constructive input and suggestions.

Management and Intellectual Property Track

10:45 AM Consortium management, structure, and operations
Facilitator: Tony Palumbo, Oak Ridge National Lab

11:45 AM Intellectual property and sponsored projects
Facilitator: Todd Pray, Lawrence Berkeley National Lab

1:45 PM Funding options for working with the consortium
Facilitator: Blake Simmons, Lawrence Berkeley National Lab

2:45 PM Molecule selection for the consortium
Facilitator: Mary Biddy, National Renewable Energy Lab

4:00 PM Advisory board roles and responsibilities
Facilitator: Jennifer Dunn, Argonne National Lab

R&D Barriers Track

10:45 AM Design: Building better biological pathways
Facilitator: Gregg Beckham, National Renewable Energy Lab

11:45 AM Build: Putting better biological pathways into new and established host organisms
Facilitators: Taraka Dale, Los Alamos National Laboratory, Adam Guss, Oak Ridge National Laboratory

1:45 PM Test: Assays and tools to understand performance of pathways in hosts
Facilitator: Jon Magnuson, Pacific Northwest National Lab

2:45 PM Learn: Machine learning and statistical methods for improving design, build, test, process integration, and scaling
Facilitator: Katy Christiansen, Lawrence Berkeley National Lab

4:00 PM Process integration and scaling: Bioprocess development and scaling, including feedstocks considerations
Facilitators: Gregg Beckham, National Renewable Energy Lab, Dave Thompson, Idaho National Lab

Synthetic Biology Foundry Industry Listening Workshop

March 15, 2016

PRE-MEETING QUESTION

1. What are the top three barriers that the consortium should address?

1.1. Getting statistically meaningful data/interpretation of data

1.1.1. in multi-variate systems it is difficult to find clear trends and people can jump to conclusions that are not statistically relevant or where correlations are mistaken for causation

1.1.2. yes (duplicate – 3)

1.2. high efficiency/highly automated routine laboratory work processes

1.2.1. yes (duplicate – 4)

1.2.2. This is only difficult if you have not done it. For those that have, and have implemented systems the control and accountability are the selling points for their products.

1.3. interface with industry

1.3.1. yes, specifically around IP. Companies are going to want assurances that they will retain full IP and that their IP is protected from others using the service

1.3.2. The Model used by the Royal Institutes in Sweden are a good method for handling IP. They don't pursue IP protection at all. This sets that companies at ease.

1.3.3. Yes. Interesting to know what industry finds important in the areas of sustainability, economics, market.

1.4. Proactive interaction to access knowledge of what really matters to industry to avoid developing technologies that later have no commercial interest or outlet.

1.4.1. Yes

1.5. developing systems / data that can be easily interpreted and used by industry

1.5.1. yes (duplicate – 2)

1.5.2. Yes, want the output to be picked up and used

1.6. finding relevant systems to develop

1.6.1. yes, don't put the cart before the horse. It will be critical to understand the eventual goal of the project. If the final goal is manufacturing, then getting the correct organism at the start, with an understanding of the process challenges will be critical (i.e. acid tolerance, thermotolerance, metabolic restrictions, aerobicity, etc)

1.6.2. yes

1.6.3. Comment 1: A group of organisms is equally likely given the strengths of each.

1.7. Having relevant scale-down models for processes like fermentation

1.7.1. fermentations can be quite lengthy and have a high statistical variation as well as high potential for

outliers. often this is a bottlneck in a program whereas micrometer plates don't give the information needed

1.7.2. Garbage in = garbage out. you need to be able to show potential collaborators that any screen applied (either small scale fermentation or microtiter plate) is representative of the ultimate scale/process used. This is especially important for microtiter plate based screens

1.8. working effectively across multiple geographical locations

1.8.1. diversity is great and having a global company has many benefits, but also many challenges

1.8.2. Avoid it if at all possible. Have centralized teams in geographically desirable areas. i.e. California.

1.9. Access to patient capital for scale up

1.10. Affordable and large scale sources of cellulosic sugars

1.10.1. This is an issue today. We just had one of the large manufacturers in China go out of business, driving the prices up and making even high value materials difficult to build economically.

1.11. Attracting talent away from the hot companies that can knowledgeably coordinate activities will be difficult.

VISION FOR THE CONSORTIUM

1. What are your thoughts on the overall goal and objectives for the consortium?

1.1. Assist the national labs to identify areas of real interest to Industry.

1.1.1. supporting tool development is an excellent idea. Helping to export standardized processes and other typical knowledge is also good.

1.1.2. tools take 10s of millions of dollars to build these tools. may exist in large company. will there be expertise from companies that have already built them. can learn from them. don't want to reinvent the wheel.

1.1.3. remove perception that working with national labs is super expensive

1.1.4. do things that are 'up there' and 'ahead of the curve'. many companies can't do this as don't have the resources

1.1.5. figuring out cost structure is huge. solutions to IP issues are hard to envision.

1.1.6. enzyme discovery; pathway discovery would be huge for all scales of companies.

1.1.7. can't duplicate what is already going on in industry. Cloud company models would be important to integrate

1.1.8. what is key integrating fact in comparison to what is already currently going on in industry and national labs

1.1.9. can a flexible enough infrastructure be built to respond to diversity found in industry to test scale-up?

1.1.10. only few unit operations are standardized today. real opportunity to standarize ENTIRE process.

e.g., cost models don't exist for separtions. Or are these things locked behind closed walls?

1.1.11. separation and purification are true bottlenecks. great areas for DOE investments

1.1.12. no overarching vision. field has not done well. Lots of failures can be pointed at.

1.1.13. fee for service should not be done at national labs. need to be 'much further ahead'. think longterm into the FUTURE.

1.1.14. want national labs to be much more relevant to industry. get away from NSF point of view.

1.1.15. industrial relevant but also benefit humankind. concentrate on problems that industry cant get done.

1.1.16. can we onboard a bunch or organisms with a lot of tools. Avoid companies needing to license and go into different organisms to avoid IP issues

1.1.17. need to stick to industrial robust organisms.....

1.1.18. expand host range and make new organisms scalable would be super helpful. Great use of national lab resources

1.1.19. or at least test new organisms at industrial scale

1.1.20. blended set of molecules needs to be considered. Future targets are likely not single molecules. a fuel, a composite.....consider as a long term goal.

1.1.21. new industrial host organisms: how long does an organism stay new?

1.1.22. big companies could quickly absorb them. May need to open source them quickly. open source is a curious biological question. is open source open source?

1.1.23. what open source model should be used? government does not sell products, however, just processing.

1.1.24. TEA could be much more automated

1.2. The three biggest challenges facing industrial biotechnology to date have been: 1) Optimization of microbes to reach industrially relevant metrics 2) Successful scale up and access to capital to scale up facilities 3) Integrated process development

1.2.1. sharing of best practices (they are in industry not in academia right now).

1.2.2. research is currently going over well trod ground as far as indsutry is concerned. accesssing harder feed stocks for instance would be great

1.2.3. in multi-variate systems it is difficult to find clear trends and people can jump to conclusions that are not statistically relevant or where correlations are mistaken for causation

1.2.4. separate innovation from operations. Labs/academics good at innovation; companies good at operations.

1.2.5. keep all of downstream operations in line within foundry and center scale up in industry.

1.2.6. get as close to drop-in as can is important.

1.2.7. 'close' is not good enough. Need exact drop-ins

1.2.8. don't be too specific. need to have good ways to identify links to industry across lab space

1.2.9. standardized tools would be super helpful

1.2.10. smaller companies need access to tools. larger companies have them, but need to know standardized tools available that can be leveraged

1.2.11. see user facility and bioprinted self factory; precommercial. How to share in? May take 20 years to do.

1.3. How many simultaneous projects can the consortium handle?

1.3.1. I'd like to see scores of projects in smaller units rather than a few large projects

1.4. Concept really powerful. What is timeline for transition of platforms or processes to industry?

1.4.1. adopting smaller timelines should be a desirable goal, not based on the length of funding cycles.

1.5. Should the model for the foundry be all work is open source; open innovation model? Labs will not have any IP associated with development of new hosts?

1.6. helping small agile companies is an easy niche to enter here.

1.6.1. workshops would be great, such training is hard to get.

1.6.2. Create go to sources building the bioinformatic tools for improving the genetic, and metabolic tractability in multiple hosts as it relates to scale-up solutions to common problems.

1.7. how will different industrial collaborations be prioritized?

1.7.1. there should at least be a quota set for both Academic and Industry (small and large) collaborations.

1.8. Lofty goals that are very worthwhile and will provide tremendous value if, and that's a big if, it can be pulled off successfully

1.9. how will intellectual property and other assets be shared

1.9.1. this is critical for industry participation

1.9.2. the ABPDU model has worked well for us

1.10. great idea -much needed. Lots of details to work out around IP, speed, how to work together etc but would really has potential to speed products to market.

1.11. Will the focus be on US companies since it is associated with US government funding?

1.12. Need to identify the appropriate points of interface between National labs and industry

1.13. to get industry participation, potential partners are going to want answers for the following questions:

1.13.1. IP confidentiality and security. access to some tools created at the foundry

1.14. Getting the capital costs and time for starting a biotech company is essential for being able to rapidly test bioman ideas. Currently, it seems like start-ups get one shot (one market, one molecule)

1.15. General goal seems to be ambitious. Unclear what it will provide that is not already available in industry or academia?

1.16. What are their timelines for deployment of an operational FAB? What services will it offer? What's the predicted cost and cycle time?

1.17. Y

1.18. With facilities (national labs) located across the country, what is the managerial strategy for limiting redundant work while ensuring proper integration of complex unit operations?

1.19. On innovation vs operational role of the foundries: I think the national labs like to think of ourselves as able to transition innovation to industry/operational use. We need to do a better job of that though.

1.20. Standardized tools would be helpful including those for TEA. Assumptions can be apples/oranges - need to operate out of a single place.

1.21. enzyme discovery / pathway elucidation could be a unique value-add

1.22. what differentiates this "foundry" from fabs in industry at Ginkgo, Zymergen, Amyris, Intrexon, etc. How do we ensure foundry does not "compete" with industry?

1.23. Standardized separations technology would be valuable add-on

1.24. What is the over-arching vision to enable / allow for bioeconomy in light of company and technology failures that have occurred?

1.25. Addressing regulatory framework to shorten time to market?

1.26. GRAS clearance on new hosts

1.27. Bridge gap between academia and industry on alternative hosts, etc...

1.28. Separation and purification is a key bottleneck. This is a role for the national labs to test separation and purification technology.

1.29. Clarity in what each lab offers is critical to communicate. Also, what is the business process for contracting with one or more Labs? What is the cost structure

1.30. Expand the host range. and develop new hosts. Could be long-term game changing. Some academics publish saying that htey are looking at robustness, but solutions are so expensive they would never happen. Here the NLs can fit in - can go a bit beyond the academics. There's only so much you can do in a grad student thesis - but NL can dig in deeper.

1.31. how to tackle the problem of optimizing the production of a complex mix of chemicals

1.32. How do we do open source right in bio? And, which flavor of open source is most relevant?

1.33. Perhaps consider molecular consortia as eventual targets for production vehicles from the foundry as opposed to single molecule

2. How can the Foundry concept address the needs of industry?

2.1. One area I see industry really using this service, and one that would leverage existing DOE knowledge/strengths is in the discovery of pathway elucidation and enzyme screening. industry often doesn't have time and resources for discovery research. The DOE has tons of sequence information from

lots of interesting organisms. Industry would be more than happy to pay the DOE $100 K to find an enzyme with specific properties that is IP free.

3. How can the national labs work on process integration and scaling to address the needs of industry?

3.1. Scale up needed - want to translate proof of concept. Metabolic engineering strategy as well as scale up. Many things need to be integrated right up stream. Impurities could be engineered out earlier on in the process. Upstream integration is critical in the beginning.

3.2. A lot of thought is being put in the scale up of fermentation, however little focus is on developing DBTl cycle for separations-a economics killer for many biorefineries. Standardizing these separation processes (only a handful unit operations exist today) to remove a standard set of impurities that exist in standardized feedstocks would be a good start.

3.3. The Labs need to be translate between science/innovation (academic research) and application/operations (industry). The burden then on the Labs is to be an effective integrator upstream and downstream. Siloed foundries envisioned as separate from the upstream SBF and separate from the downstream Industry customers is a troubling starting point.

3.4. you may want to reach out to the USDA - they have a mission to exploit ag by product with no commercial current use.

3.4.1. Good point - sinlge thread support from DOE could be tenuous, especially as products are initially unlikely to be energy

4. Would consortium also focus on non-traditional hosts?

4.1. yes, this is going to be critical for industry. often manufacturing will require special organisms with unique properties . that being said, you will still need to focus on "platform" strains. so a handful of organisms that represent a broad range of metabolic space and manufacturing potential. you can't reinvent the wheel every time

5. Are multiple organisms in chained transformations being considered?

5.1. I dont think this has been mentioned in the discussions. Is it needed?

5.1.1. Regulation of a single organism to go all the way to the desired product, as we have seen today, provides unique challenges. Multiple organisms may be needed for robust systems of manufacture.

5.1.2. capex for such a system could be prohibitively expensive, if you need a series of tanks, essentially doubly or tripling capex costs. Not off the table, but you need to think very carefully about what the manufacturing implications of such a strategy would be.

MANAGEMENT AND INTELLECTUAL PROPERTY TRACK

1. 10:45 AM - CONSORTIUM MANAGEMENT STRUCTURE AND OPERATIONS INCLUDING DATA MANAGEMENT - Facilitated by Tony Palumbo

1.1. Are there exemplars of consortium management that work well for industry? What works best in your experience?

1.1.1. We have had good experiences working with ABPDU

1.1.1.1. because the staff has worked in industry its been very helpful

1.1.2. We have a great exemplar in the UK's Advanced Materials Research Consortium: http://www.amrc.co.uk/work-with-us/membership-model/

1.1.3. Is research driven by the Labs or by industry?

1.1.3.1. what are the incentives for the staff? are they publication driven or are they project completion and milestone driven?

1.1.3.2. I have seen a bunch of innovation efforts in industry and academia and cultural comparisons can be made to make an effort to tackle culture. I can be talked to [ron shigeta]

1.1.4. Culture is key - recommendation to not make it too esoteric / adademic.

1.1.4.1. Comments from group: Needs to be addressed upfront. This is one of the challenges with efforts by academics.

1.1.4.2. modern management literature on this is extensive

1.1.4.3. must be a new approach for a new economy

1.1.4.4. bring on people from industry to work here - that should help change culture

1.1.5. Avoid turf wars and ego-driven interaction

1.1.6. Real time tracking of progress and impact on dependent tasks would be very useful. Transparency in how things are connected and how delays in one unit op impact timelines for another unit op is critical. I would recommend a live and interactive Gaant chart (or a similar tool) such that each key stakeholder can immediately see and communicate changes in timelines.

1.1.7. Have to align incentives, goals, to make the culture work well. E.g. concern that it could be driven by Lab incentives to monetize IP...

1.1.8. Comment from group: There has been success in consortium Pre-commercial -- industrial only -- tiered levels. Hybrid approach works well on what kind of participation

1.1.9. Concern around certain consortium members having too much influence on overall direction and priorities

1.1.10. Quota system / steering committee to govern resource allocation across companies?

1.1.10.1. Mission needs to be clearly defined.

1.1.11. Make sure staff goals align with project goals -- not just focused on publications but really driving towards goals of efforts

1.1.11.1. Have a report card to track achievements.

1.1.11.2. have the staff extremely aware of the IP and agreements when evolved in industrial projects

1.1.12. Concern around mission of the entity and that it could be used (inappropriately) to further research goals of individual lab researchers.

1.1.13. Labs have the opportunity to share best practices approach

1.1.14. Can the consortium serve develop dissemination of best practices such as workshops, training, etc.

1.1.15. Maybe bring in leadership from industry?

1.2. What management structures create problems?

1.2.1. Quota system - to balance influence of large companies v small companies. NL management needs to be committed to goals of the project.

1.2.2. Report card to track progress. Could be impossilbe in some federal fundign situations.

1.2.3. Pre-competitive yes/no.... The expectation of this organization for the miession has not been decided.

1.2.4. How can you be everything to everybody?

1.2.4.1. Don't want to take on so much that you don't actually do anything.

1.2.5. Virtual open innovation center - core technology - industry can come regardless of what industry needs - an dyou can solve the problem.

1.2.6. HOw can you be nimble so that you're not outdated before you launch?

1.2.7. Should national labs be a CRO for industry? NL people need to work on enabling problems for mid- to long-term. NL shoudl not work on one product b/c one company wants it. Coudl be data management? Common impurities across fermentation.

1.2.8. Woudl be nice to have some larger companies involved that make products. Do we lose something by not having larger companies involved at this point?

1.2.9. Target molecule...e.g., glucose already exists. But the concept of a target molecule may be too optimistic?

1.2.10. Need a better way to capture volatile products - that would be a game-changing development.

1.2.11. Biology has raced ahead of our abiliity to screen. LIkes idea of automation and high-throughput screening. If there is a separations step, it is not high-throughput. Government labs should work on assay technology b/c they already make a lot of stuff they cna't screen.

1.2.11.1. Need to look at more R&D to consider assay and considering detection for high throughput screening.

1.2.12. Need help on automation, hard ware. Perhaps racing to front end to do biology may not be the best approach. Need to be able to screen.

1.2.13. Overall objective: enable bio-based chemical industry. How do we enable this industry to get more products to market?

1.2.14. Is the best way to help scale-up, assays, biology?

1.2.15. Mission: shrink cost and time from idea to market. There are many ways that we could address this mission.

1.2.16. Does DOE compete with comanies that are doing the same thing. Is DOE setting up a competition. REG started out as a platform company making molecules that could be iterated into other molecules.

1.2.17. Really serious concerns noted around creating competition with industry (for example Lab project competing with industry projects on specific products).

1.2.18. Question around how to integrate academics into the consortium - outreach and education to "catch them up" and get them involved.

1.2.19. Need an industrial person high in the leadershipo.

1.3. How should decisions be made on which molecules should be targeted and which organisms should be used?

1.3.1. How to allocate b/w strain engineering and scale-up tasks - need to balance.

1.4. Additional Comments

1.4.1. Define the mission of the organization - this is critical

1.4.2. How can you be everything to everyone?

1.4.3. Difficult to build a successful model on a scale-up because you are playing in their sandbox.

1.4.4. Open innovation center - industry can come and problems can be solved. Human assets, plus other assets (like fermentors)

1.4.5. Disseminate best practices. Rather than everyone redoing their own work. Then people can focus on something bigger than the basic problem that has already been researched by one group.

1.4.6. A product should not be associated with this.

1.4.7. How do we enable the development and deployment of bioproducts. What is the best way to enable the industry.

1.4.7.1. Reduce the time and costs it takes to move a product to market.

1.4.8. Does DOE go out and compete against industry that is already doing this?

1.4.8.1. Bottlenecks have already been identified. It is an opportunity to pull together resources.

1.4.9. Look at projects that are very far in the future.

1.4.9.1. DOE to help in more efficient way that enable faster deployment of technologies

1.4.10. End Result: Deploy – Commercialize

1.4.11. Fundamental mission should be to enable industry to deploy

1.4.12. Most people don't realize how much money has already been spent on research. This could provide an opportunity to bring to light. Even playing field.

2. 11:45 AM - INTELLECTUAL PROPERTY AND SPONSORED PROJECTS, INCLUDING CRADAs, WFOs, MTAs, NDAs, IIAs, etc. - Facilitated by Todd Pray

2.1. What are the barriers to working with the labs?

2.1.1. Understand what the labs do

2.1.1.1. what role do they play?

2.1.1.2. labs have a depth of experience because they touch so many industries. It is a huge value.

2.1.2. How to access the labs

2.1.2.1. Easy POC – liason

2.1.3. Understanding what the labs do and how to access it. What are processes for collaboration. Need a menu or roadmap for what labs are doing. Need points of contact - omsbudsman.

2.1.3.1. Streamline would be very useful

2.1.4. If the government is funding a project - should there be IP sharing? That would be a deterrent/hindrance. Issue can be overcome iwth a negotiated contract over IP.

2.1.5. Perception that lab people work more on their own projects than those relevant to industry. Just keep in mind that this is contract manufacturing servie for partner (?). Show objective is to enable industry, not to just fund a post-doc who needs a paper.

2.1.6. SOW has been above market price, but incubator FOA was good - good test bed - to get industry more familiar with the labs. (SBV)

2.1.7. GIve this program the flavor that it is industry-centric.

2.1.8. Industrial consultants become valuable b/c they work iwth many different companies. IN this way, the labs have an advantage b/c they have a lot of experience working with many companies.

2.1.9. Is there an expectation of exclusivity. Does company pay for exclusivitiy to reduce risk that someone else will come in after them to work on that molecule?

2.1.10. IP: freedome to operate and competitive advantage

2.1.11. Perception around IP and Cost

2.1.12. What is IP perception: can't work with natinoal labs b/c they will take IP. OR national labs are doing their own thing with no connection to what we want.

2.1.12.1. Could they get more efficienct results when working with industry

2.1.12.2. Price can be higher than standard market value

2.1.13. As many things are funded by royalties, this may be difficult.

2.2. What kinds of agreements need to be in place to feel comfortable working with the labs?

2.2.1. Open source (everyone has already done CRADAs, WFO). You should want to be different. Sell yourself differently to be attractive

2.2.2. two different approaches -- foundational approach and then silo that IP to utilize that IP for individual case

2.2.3. Find the right model that works for the IP

2.2.4. Needs to be a flexible way to work. It is about culture considerations

2.2.5. Perhaps the small business voucher approach is the best way to set this up.

2.2.6. A dedicated group needs to be assigned to address IP.

2.3. There are two principal types of project agreements when industry works with National Labs. Please comment on any specific concerns and opportunities under each structure:

2.3.1. Cooperative R&D Agreement (CRADA): typically occurs when there is cost share by the Lab and the company. Under this structure IP ownership is based on inventorship, and shared IP ownership can result. Industry sponsors can typically access exclusive licenses to any technology developed where Labs may own IP.

2.3.1.1. Concerns

2.3.1.1.1. Industry can be wary of joint ownership approaches, even where exclusivity is offered. The challenge is in ensuring appropriate protection is sought, and a coordinated approach to defense of IP. These "future" challenges need to be clearly thought through and agreed up front.

2.3.1.1.2. Why do all labs need to be involved.

2.3.1.1.2.1. Geography considerations. Availability of existing resources.

2.3.1.1.3. How do we learn but not infringe on IP

2.3.1.1.4. Concerns about paying for R&D and the have leakage issues not of IP but more of learning

2.3.1.1.4.1. Basically, later projects get the benefit of learnings from earlier projects.

2.3.1.1.4.2. Can't un-know what you know

2.3.1.1.5. Joint ownership is very difficult, especially defining things down the road.

2.3.1.2. Opportunities

2.3.1.2.1. Need to have confidence that this is being run efficiently.

2.3.1.2.1.1. Try to centralize as much as possible.

2.3.1.2.1.2. Industry is virtual and global. This consortium can mirror this.

2.3.1.2.2. First right of refusal

2.3.1.3. Other Comments

2.3.1.3.1. Given the breadth of R&D within the consortium. This could be an open access/source opportunity that allows more opportunity

2.3.2. Work for Others (WFO): project agreement typically governs projects when industry fully sponsors the research at the Lab. Under this structure the industry partner may be granted title and ownership to inventions and IP, irrespective of inventorship.

2.3.2.1. Concerns

2.3.2.1.1. This does not seem to support the mission of the consortium.

2.3.2.2. Opportunities

2.3.2.2.1. Right to retain title (IP)

2.3.3. The Agile Biomanufacturing Consortium will have several National Lab and industry participants. This may raise concerns for individual industry users around data management, access to background (pre-existing) IP at the Labs, and how access to new IP generated in the consortium and on individual will be defined. Please share your concerns and potential solutions on the following:

2.3.3.1. Access to background IP

2.3.3.1.1. It would always be of interest to a company to see if it is lower cost to license technology instead of developing

2.3.3.1.1.1. In practice -- how common would this be.

2.3.3.1.1.2. Perhaps areas to be part of a service

2.3.3.1.2. Is there different background IP

2.3.3.1.2.1. Need background IP to start project

2.3.3.1.2.2. Background IP that goes into R&D purposes -- not necessarily for running process

2.3.3.1.2.3. What gives me freedom to operate and competitive advantage

2.3.3.1.2.4. Freedom to operate is critical

2.3.3.1.2.5. Cascade of fees

2.3.3.1.3. Make process simple and have a single point of negation

2.3.3.2. New IP allocation and level(s) of exclusivity

2.3.3.2.1. There are a lot of grey areas here. Need to make sure things are spelled out.

2.3.3.2.1.1. How to deal with situation when company x comes to ask for a molecule to be developed and then 6 months later company y ask for the same molecule. This could be a challenge when working towards first to file IP.

2.3.3.2.1.2. Do we need exclusivity considerations

2.3.3.2.2. NNMI blanket IP considerations based on level of funding/commitments

2.3.3.2.3. Consideration on which organization and underlying IP requirements -- differences

between which company runs labs

2.3.3.2.4. This should be verified: Operator has first option, then DOE, then inventor.

3. 1:45 PM - FUNDING OPPORTUNITIES FOR ACCESSING THE CONSORTIUM - Facilitated by Blake Simmons

3.1. What kinds of financial methods should be in place for accessing the consortium? (e.g. company's own contribution, set aside for specific projects like technology development, etc.)

3.1.1. USDA bio based center

3.1.2. Sustaining funding

3.1.3. FOA - how would you want to see something structured around this consortium

3.1.4. Grant applications

3.1.5. Competitive proposals

3.1.6. Single POC to connect folks

3.1.7. Part of the Foundry operating as a user facility

3.1.7.1. this is publicly available data at current user facilities, though

3.1.7.2. not guaranteed it will be done - when bandwidth is available

3.1.8. is there a way to set up a membership of foundry by type/size of company. a small company can "buy into" foundry based on size or revenue- they get a head of big company with more money if not member.

3.1.9. state funding

3.1.9.1. will probably only come in if it impacts there state

3.1.9.2. start with the states the labs are in

3.1.10. Must have a person that can be talked to...right away

3.1.11. philanthropic funding - Sloan foundation as an example?

3.1.12. NGOs, foundations - clear benefit to society needs to be articulated

3.1.13. funding around collaboration efforts

3.1.14. "moonshots" to help fund the foundry around infrastructure e.g. for rapid antibiotic development

3.1.15. leveraging state funding for industry projects at foundry?

3.1.16. Gates billionaire foundation - basic science

3.2. Please discuss prioritization (e.g. jumping the line for significant cost-share, etc.)

3.2.1. tiered models

3.2.2. customers who pay more, get results faster

3.2.2.1. paying for more resources to put on your project

3.2.3. concern around well-resourced companies blocking smaller ones from getting access or fast turnaround

3.2.4. sliding scale - people in different economic buckets

3.2.5. make a user friendly website and person available to disseminate information...

3.2.5.1. government and public affairs person/group

3.2.6. can the Labs help in more of a public affairs / gov't relations aspect (e.g. around inter-agency funding and regulatory opportunities)

3.2.6.1. coordinate language and vision with the coordinated framework

3.2.6.2. Not glossing over the IP requirements

3.2.6.3. Position dedicated to what the Foundry is, benefits, why are we doing it? Outreach role

3.2.6.4. Internal/external education/advocation

3.2.7. OSTP input session in Davis on March 30 on bioengineering

3.2.7.1. Katy will distribute to the group

3.2.8. Be sure we don't under-resource IP. Have a person available for public outreach

3.3. What kinds of facilities would companies like access to?

3.3.1. Public perception - language not consistent with coordinated framework. Need common language etc across various regulatory agencies. This effort should be well-coordinated with what is going on across other agencies. White House is coordinating fo rnow. Needs to be an element of stakeholder engagement. Input session in Davis on bioengineering.

3.3.2. External facing piece: position dedicated to what Foundry is, why are we doing it, the beneifts for individuals and society. Someone who knows how to communicate to the public and help communicate. JBIE and BESC have one. Model to follow within DOE. Although...people should talk to scientists internally what is going on.

3.3.3. Coudl philantrhropic org be a funding source. Not a lot of money in philanthropic space - Sloan Foundation is the only one really funding.

3.3.4. How does it benefit conservation, health, society

3.3.5. State funding?

4. 2:45 PM - MOLECULE SELECTION FOR THE CONSORTIUM - WHAT ARE GOOD PROOFS OF CONCEPT? Facilitated by Mary Biddy

4.1.1. Did you determine whether or not the suppliers were sole source?

4.1.2. Splitting your long, medium and short term targets by functional replacements (long) and drop in (short or medium) time frames.

4.1.3. Should the foundry focus on DOE-relevant targets and/or company-focused targets?

4.1.4. Question was raised on why would the Labs work on "commercial" targets (e.g. succinic acid)

4.1.5. should have heavy input from industry

4.1.6. annual refresh of "beach-head" or top 10 molecules...

4.1.7. let advisory board decide priorities on molecules and assay technology

4.1.8. some comments in the room were more focused on enabling technologies and software as desired outputs than developing specific "products"

4.1.9. built-in performance metrics

4.1.9.1. DOE must show there are targets and that carbon (e.g.) is being reduced.

4.1.9.2. beach head concept

4.1.10. Prove chiral center introduction. Hard carbohydrate transformations. Large molecule methods. Surface active molecule production.

4.1.11. broadly enabling customers, however, have mechanisms that also support narrow research for customers

4.1.12. Broadly applicable tools and the ability to service small businesses that do not have money from their venture team.

4.1.13. Metrics

4.1.13.1. Greenhouse

4.1.13.2. land use

4.1.13.3. water

4.1.13.4. availability of sourcing

4.1.14. what is the best surrogate to tackle the challenge

4.1.15. Platform that has flexibility to make multiple products - this may give DOE what it needs. It doesn't need to be just about fuel.

4.1.15.1. goal should be core technology infrastructure

4.1.15.2. Go after the beach head molecules

4.2. What decision criteria should be evaluated when choosing molecules for the consortium?

4.2.1. Developing pathways to overcome challening conversion

4.2.2. sole sourcing of a single product -- supply chaing ocnsiderations

4.2.3. Reduce supply risk

4.2.4. Hard to make carbohydrate combinations.

4.2.5. targeting transformations

4.2.5.1. national labs should not be the ones picking specific targets

4.2.6. expand reagent based methodologies

4.2.7. develop assays to enable high throughput screening

4.2.7.1. reason people do not work in this area because not publishable and not fundable -- it is needed tool.

4.2.8. Data integration tools that are government sponsored freebies

4.2.8.1. avoid costly data requirements for omics platforms

4.2.9. Can you provide an assay to with every translational step.

4.2.10. translation R&D -- need horse power to get it through faster when VC funded -- need to get to product fast -- save enough money to get through faster

4.2.11. Adopt strategy to go after really hard to do things

4.3. Are there molecules/applications that the center should not consider? Why?

4.3.1. Specific molecules should not be pursued. Classes of molecules and fundamental transformations would be better.

4.4. Are there any specific applications that the center should develop molecules to support? For example, molecules which can be utilized for polymer production.

4.4.1. Concentrate on tool development and fundamental transformations rather than specific molecules. Applications to stay away from include places where the industry will do it for themselves.

4.4.2. Food - moving food around the globe costs fuel

4.4.3. Protiens

5. 4:00 PM - ADVISORY BOARD ROLES AND RESPONSIBILITIES, INCLUDING CHARTER - Facilitated by Jennifer Dunn

5.1. What have been your most valuable experiences either serving on or working with an external advisory board?

5.1.1. Being on: Science and Technology evaluations team for acquisition of new technologies and implementations of others at Illumina

5.1.2. Working with: Assembling a list of talent required on a science advisory board and then using them to the best advantage for getting the right products built and the right technologies to build them.

5.2. What would you add to this list of potential functions of an advisory board?

5.2.1. Allow leadership to test out ideas (sounding board)

5.2.2. Inspire change in the organization (structure, direction)

5.2.3. Keep consortium on track with respect to project plan

5.2.4. Provide stakeholder perspective

5.2.5. Give feedback on technical approach

5.2.6. Provide real-world guidance regarding market and regulatory conditions

5.2.7. Help leadership plan for the future

5.2.8. Advise on intellectual property issues

5.2.9. Provide feedback in how consortium is communicating with stakeholders

5.2.10. Help the Nat. Labs build equity in industry which they do not currently have.

5.2.11. Have a cadre of people to use for technology and science evaluations.

5.2.12. Evaluate proposals

5.2.13. Help figure out IP challenges (especially if the INdustry is well represented on the board)

5.2.14. Mission clarity is essential

5.2.15. Need clear direction from mission, where are things supposed to go so that the board can facilitate direction (can't get somewhere if you don't know where you are going)

5.2.16. Deciding priorities of beach heads, technical role (guidance) (See 20, this seems more approriate for Board of Governors)

5.2.17. Charter for Foundry

5.2.18. Separations vs assays vs beach heads

5.2.19. Determine how companies engage and pay for "premium" membership

5.2.20. Board members need to have skin in the game (incentive, culture)

5.2.21. One or two boards? 1. Board of Govenors (industry) 2. External Advisory Board (could have industry members)

5.2.21.1. Advisory board - non voting

5.2.21.2. Need to be careful if industry BOG/Advisory have access to info from other companies (maintain confidentiality

5.2.21.3. Have academics sign NDAs, more difficult for industry

5.2.21.4. There are BO Directors that follow ethical values/integrity/legal consequences, and do not disclose, for the most part this is achievable to have BOD be industry members

5.2.22. To set up a foundry you need to operationalize biology. To not have industry members on the board could relate into re-inventing the wheel, and then result in industry not becoming invested in the foundry.

5.2.22.1. Asking the proprer role of Board, is that too into the weeds

5.3. Do you think the Biofoundry should prepare a charter for the EAB?

5.3.1. Yes, what would make up the key elements of the charter?

5.3.1.1. Frequency of meetings

5.3.1.2. Type of feedback requested of board

5.3.1.2.1. *At least 4 times per year.*

5.3.1.3. Expectations regarding compensation (e.g., travel expenses)

5.4. Are there any existing charters we can use?

5.4.1. The Jason's

5.4.1.1. Industry

5.4.1.2. Academic

5.4.1.3. they aren't taking the things back and profiting because it is not allowed from the get go - made

very clear in the charter

5.4.2. IPAs

5.4.2.1. Would be some one in academia

5.4.3. BRDI

5.5. How do organizations with advisory board members view/handle a charter?

5.5.1. EAB members can sign with their affiliations

5.5.2. EAB members cannot sign without corporate/organizational approval

5.5.3. More than twice a year for the beginning of the year. Physical meetings twice a year, but at the start more remote meetings

5.5.3.1. $35M investment, multiple meetings for fudiciary oversight. At least quarterly

5.5.4. What should the term of membership be? Should it be rotated? Should it be staggered?

5.5.4.1. Three years. Yes and Yes

5.5.4.2. BRDI is 2 years and staggered

5.6. **What advice would you give to the initiative as we recruit and begin to work with an external advisory board?**

5.6.1. make sure to recruit experienced industry people

5.6.2. multi-represented

5.6.2.1. seasoned members

5.6.2.2. Biology, Chem E

5.6.2.3. Society rep- NGO

5.6.2.4. Academics (outside national labs)

5.6.2.5. Deployment of Technologies at NGOs (like Gates Foundation)

5.6.3. Industry cannot make decision for the government, industry can advise, and then Feds take actions (FACA)

5.6.3.1. National labs also can't make decisions for the government

5.6.3.2. nat'l labs would make decisions for consortium not government

5.6.3.3. If the Governing Board makes decisions for the Consortia and not the federal government then industry and national labs can make the decisions

5.7. **What is an appropriate size of the board?**

5.7.1. 10-14 is average.

5.7.2. the more people, the more squabbling

5.7.3. Is that too large? Efficiency often leads to smaller groups doing the work

5.7.4. should have odd number for tie breaker

5.7.5. should be most broadly extensible range

5.7.6. What is the appropriate balance of technical expertise and commercial/public reps

5.7.7. 9 is preffered over 14. Lots of consensus around that

5.7.8. How do we avoid Board Fatigue?

R&D BARRIERS TRACK

1. 10:45 AM - DESIGN: BUILDING BETTER BIOLOGICAL PATHWAYS FOR PRODUCTS - Facilitated by Gregg Beckham

1.1. What are the biggest barriers for designing new biological processes?

1.1.1. high throughput gene synthesis

1.1.1.1. outsource to industry is current model. Expected to stay the same within Foundry

1.1.1.2. turnaround time is important

1.1.1.3. one example using 1.8kb cut off to outsourcing versus in house.....time is killer. inhouse might be faster???

1.1.1.4. foundry may be able to capitalize on JGI resources. Current consortium using JGI processes

1.1.1.5. 1.8 kb is a cut off as this is a great sweet spot for outsourcing. It is nearly impossible to to outsource 2000 constructs at 20 - 30 kb in length and get them back within 3-4 weeks

1.1.1.6. would be helpful to have a thermophile in inventory to work with. How hot? within the realm of not having to cool it.

1.1.1.7. that said, the capabilities to generate this type of high throughput synthesis of relatively large constructs mentioned in comment 5 is available for companies with a lot of CapEx investment

1.1.2. host onboarding

1.1.2.1. thermophiles or other hosts that match process and separations

1.1.2.2. don't spread too thin.....go unique for extreme pH or extreme temp?

1.1.2.3. promoter range, terminator sequence known and verified? scaled?

1.1.2.4. what is spec sheet for 'on-boarded organism'

1.1.2.5. how to deal with "parts" for a variety of hosts

1.1.2.6. tiered specsheet for what it means to be onboarded. different levels of onboarding likely the result

1.1.2.7. effort for onboarding or organisms likely going to be HIGHLY distributed throughout labs

1.1.2.8. locus of integration

1.1.2.9. prokaryotes easy; test all promoters for ~$0.5M

1.1.2.10. rapid methods for parts validation

1.1.3. design phase- pre-screening- what gets considered

1.1.3.1. focus more on regulatory and IP? easy to export products. highly recalcitrant. length of pathway dictates organism. use advanced tools (e.g., flux/balance analysis). toxicity issues

1.1.3.2. pathway elucidation. IP-free enzymes!!!! find alternates that catalyze same reaction.

1.1.3.3. different industries focus on different aspects

1.1.3.4. S&P500 fund analogy

1.1.3.5. pathways: elucidation, length, enzyme variants, combinatorial testing

1.1.3.6. toolkits and characterized range of similar enzymes (e.g., P450 spectrum)

1.1.3.7. need reliable, cheap database of enzyme evolution. completely random and saturated mutagensis screening

1.1.3.8. just need to go to market. chemical outcompetes bio processing if known pathway, even if 100 steps. bio path no gauranteed or predictable presently

1.1.3.9. library of P450 mentioned again. think to be a very useful tool!!!

1.1.4. Use of GMO algae is restricted in some areas

1.1.4.1. optimize whole system response.

1.1.4.2. genetic manipulation but use endogenous gene set(s)

1.1.4.3. very constraining and needs different thought processes

1.1.4.4. could change if regulatory environment changes

1.1.4.5. To be clear, algae in Hawaii cannot have exogenous DNA. The algae field can and does use engineered organisms

1.1.4.6. Gene editing techniques may provide a non-gmo alternative, but they need to be developed

1.1.4.7. To put an even finer point on it, some algae companies even in Hawaii can use GMO algae. Use depends on which island/county

1.1.5. Excretion is an important goal for engineered systems

1.1.6. approach to life cycle assessment

1.1.7. how to deal with GMO issues

1.1.7.1. designing organisms that relieve regulatory hurdles downstream is HUGE

1.1.8. P450's are important targets - a panel of accessible p450's would add high value

1.1.9. Within organism gene utilization to line up with regulatory requirements.

1.1.9.1. not just gene utilization- overcoming downstream regulatory hurdles

1.1.10. standardization of design and centralized and accessible location for validated enzymes and parts for a number of organisms

1.1.11. TEA LCA

1.1.11.1. have to have well defined process for this to contribute

1.1.11.2. needs a defined process

1.1.12. Too much content and not enough capability will not fly with the big companies that are already doing their own programs.

1.1.13. how would technology companies integrate?

1.1.13.1. one was exited; can't meet pricepoints; need better systems than what we have

1.1.13.2. co-developing platforms is a potential

1.1.13.3. lending software expertise and automation engineering

1.1.13.4. reward: ongoing question. no mandate to bring money back into company via this endeavor. is there much money that could come from licensing of software tools?

1.1.13.5. alternatively, there is money to be made from it. remove subjectivity from process. Increase efficiency. Worked in oligo manufacturing business. ex-illumina employees highly sought by field. remove human errors, for example

1.1.13.6. primarily by donating software, equipment and expertise to the effort to build a platform that can generate "content" that will benefit the entire community, both academic and industrial. Look hard at similar models in microelectronics. The Stanford "Nanofab" is an example of an advanced silicon foundry that helps both researchers and industry. The tech might be last generation cast-offs from Intel... but it still kicks ass and is better than anything you could build in your garage :)

1.1.13.7. extract all places for humans to 'mess up'

1.1.13.8. need $100Ms-scale for these types of technology transfers to be profitable

1.1.13.9. many examples where this has worked out. not mny startup companies are aware of when to license and when to build in-house.

1.1.14. Control drives down cost. Innovators are bad at control. We need to automate discovery, development and production in a seamless system.

1.1.15. artificial compartmentalization

1.1.16. So often we have used enzymes outside their biologically relevant parameters. Having cadres of enzymes, across a type, that will achieve the transformation with the required driving force.

1.1.17. Could leaky/toxic materials be removed by a second organism?

1.1.18. Fermentation data has not been normalized across the industries involved.

1.2. How can the field shift to “push” tools from “pull” tools?

1.2.1. can setup up discovery triggers. once you find an enxyme or set of enzymes, call and then we'll purchase what was found

1.2.1.1. same with changes in TEA or LCA analysis

1.2.1.2. what about competition? what if five companies get triggers?

1.2.1.3. but what if gets notification that something two steps away and you have the magic enzyme tht fills the gap. WIN WIN

1.2.2. want more discovery?

1.2.2.1. just make the tool and the company then uses them?

1.2.2.2. need to define pathway elucidation better. TOO BROAD?

1.2.3. balance between enabling tools and content

1.2.3.1. tools are not easy to commercialize, data is. If you take things one step farther to actually generating actionable data, you have produced something of high value... what you do at that point is another question. I would vote for that content to be made freely available.

1.2.4. can we find more conccrete capabilities that industry needs in design?

1.2.4.1. think of kinase or phosphatase screening kits. Could we build more kits like that?

1.2.4.2. alternative functions show up different conditions than those used for first defined function

1.2.4.3. artificial compartmentalization. Useful?

1.2.4.4. find functions for proteins of unknown function

1.2.4.5. ways of approaching catalytic space

1.2.4.6. general biological discovery. fill or survey functional space

1.2.4.7. enzymes with multiple function space.....when most active in what condition. optimize for cell free conditions

1.2.4.8. would companies give away this knowledge on a particular target

1.2.5. artificial compartmentalization might be a good focus as an enabling tool

1.3. How rational are current designs?

1.3.1. semi rational is very important- so much that's not known

1.3.1.1. indeed. In fact, it may be that combinatoric or machine learning guided rapid D/B/T may always be a better alternative to "rational" design in the biological context. This is not to say that more up-front intelligence is not valuable... it is just that you may not want to give up the capability of biological systems to find a novel or best solution out of many possible solutions.

1.3.2. emerging engineering discipline

2. 11:45 AM - BUILD: PUTTING BETTER BIOLOGICAL PATHWAYS INTO NEW AND ESTABLISHED HOST ORGANISMS - Facilitated by Taraka Dale / Adam Guss

2.1.1. need to consider regulatory challenges with new hosts/tools

2.1.2. don't need another E. coli

2.1.3. how do we get closer to theoretical yields?

2.1.4. knowledge generation vs. strain construction

2.1.5. how to engineer resistance to phage(s)?

2.1.6. will it take to long to get to point where current suite of hosts operate?

2.1.7. how to do flux analysis/understanding builds in a platform tool?

2.1.8. synthetic compartmentalization of biological processes in cells

2.2. Are you interested in using new hosts?

2.2.1. hosts that go beyond current benchmarks of production efficiency

2.2.1.1. fed-batch systems: how to keep them going longer?

2.2.1.2. cell systems are primitive compared to pharma

2.2.2. are processes/methods/materials too protected? Can you profit from new ideas in this space?

2.2.3. optimization shouldn't be in the vocabulary- that's what companies do

2.2.3.1. innovation vs. operation

2.2.3.2. but extending production phase, etc., does require some work with optimized systems

2.2.4. lipophillic organisms discussed

2.2.5. match organisms to endpoint(s) and process(es) envisioned for production environments

2.2.5.1. keeping organisms the same organisms. if modify too much, then the organism is not like original. e.g., Sacch at Amyris is really not yeast

2.2.6. try to get rid of sterilization

2.2.7. long production cycle. tolerant of product that it is making. minimize in-production evolution/selection

2.2.8. if would have done this 30 years ago, would possibly have 12-18 production hosts today. but we didn't and we don't

2.3. No, why?

2.3.1. Are companies committed to their hosts?

2.3.2. Would you want to improve current hosts instead?

2.3.2.1. what is really causing limitations? how to move past those limitations?

2.4. Yes, what would you be interested in having an external partner do?

2.4.1. Genetic tool development to enable engineering

2.4.2. Engineering of actual strains

2.4.3. Optimization of strains for metabolic flux

2.4.4. Optimization of strains for scale-up

2.4.5. strains with longer periods of high production rate

2.5. Would you be interested in new or non-standard organisms?

2.6. Yes

2.6.1. New bacteria

2.6.2. New yeast

2.6.3. Organisms that both degrade biomass and make a product

2.6.4. Organisms that only make the product of choice

2.6.5. Extremophiles

2.6.6. Photosynthetic organisms (Cyanobacteria, Eukaryotic algae)

2.6.7. provide differentiating result for user

2.6.8. lower cost operationally

2.6.9. need anaerobic and aerobic

2.6.10. compartmentalization issues inside cell. make the compartmentalization synthetic -- genetics, translation.....long term goals. don't want to have to live with natural compartmentalization

2.6.11. Novel eukaryotic organisms with known mating types (for genetic exchange post-strain improvement).

2.6.12. keep construction in house since may be working with proprietary strain

2.6.13. DNA and certain construction activities are becoming commodities

2.6.14. work on novel DNA synthesis technologies. LOOK AT LONG-TERM FUNDAMENTAL CHALLENGES. go high!!!

2.7. What kinds of properties do you want/need in a host?

2.7.1. Reaction conditions

2.7.2. Substrate ranges

2.7.3. TEA/LCA advantages for using the host over the traditional process

2.7.4. How many external stakeholders need to be interested in a specific organism to justify the benefit of developing a variety of metabolic flux systems and libraries of transcriptional/translational regulators?

2.7.5. want to get rid of sterilization

2.7.6. want a system that is resistant to phage

2.7.7. long production cycle

2.7.8. handle toxic products/intermediates

2.7.9. minimal evolution

2.7.10. can make more than one product

2.7.11. balance of properties between what an organism started at vs. where it was engineered to

2.7.12. known mating types

2.7.12.1. and an ability to switch off mating

2.7.13. is there a repository of what has already been accomplished in National Lab space?

2.7.14. make a database. standarized strain descriptions. growth conditions. how made. tools used. substrate ranges. how transformable? etc.....

2.7.14.1. already doing this on algal side with BETO funding

2.7.14.2. need feedback from industry to see what strain features are important to include in

database

2.7.14.3. media and cost point are important for decisions on strain selection(s)

2.7.14.4. standardization important for 'learn' exercises

2.7.14.5. too many variables at present. Comparisons are difficult!

2.7.14.6. collecting metadata will be helpful if different conditions are needed as processes mature

2.7.15. what are thoughts on cell-free systems?

2.7.15.1. first incarnation of this effort included cell-free approaches

2.7.15.2. is it used other than in basic sciences?

2.7.15.3. value: gets rid of limitation on import/export rates

2.7.15.4. used extensively for fine chemicals

2.7.15.5. worth keeping an open mind on

2.7.15.6. been around for a while. What are cost of goods using this technique? GreenLight is expander of field right now. in pilot stage on 100L scale

2.7.15.7. might tie in with microfluidic platforms in testing

2.7.15.8. do we slip micro and move directly to nano? use lab site Echo for this Foundry?

2.7.15.9. JBEI uses wave technology to build and test. paper already published

2.7.15.10. can you screen/detect at the nanoscale?

2.8. What are the biggest barriers to building new biological processes, including DNA assembly and host organisms?

2.8.1. have we moved from micro to nano? can you screen at the nano scale?

2.8.1.1. getting enough molecules to detect is one of the big challenges

2.8.2. may need more sensitive detection technologies to screen at the nano scale

2.9. What kind of work is needed for companies to trust/onboard new organisms and processes?

2.9.1. unknown: need to do omics to understand what's changing, esp. in the food space

2.9.2. pass regulatory muster

2.9.3. transormation efficiency and recombination efficiency. Reliable and robust?

2.9.3.1. can we get there with more exotic hosts?

2.9.3.2. go to organisms are not available to small startups. too energy/labor/capital intensive

2.9.4. transformation efficiency, recombination efficiency, provide data that gives confidence that process is reliable and robust

2.9.5. annotated genomes

2.9.6. what are the absolute metrics (switch points)?

2.9.6.1. tolerance/growth rates/feedstock range/process integratable/ easier to integrate rather than traditional hosts

2.9.6.2. TEA/LCA on new strains will make or break integration and usability

3. 1:45 PM - TEST: ASSAYS AND TOOLS TO UNDERSTAND PERFORMANCE OF PATHWAYS IN HOSTS - Facilitated by Jon Magnuson

3.1. What are the biggest barriers for testing and understanding new biological processes?

3.1.1. Standardization of fermentation data software/testing

3.1.2. There is always a big disconnect between the results obtained at small scale (96-well plates) and shake flasks and fermenters.

3.1.3. sooo much data. so underutilized

3.1.3.1. open up all proprietary data formatting so data can be more easily utilized

3.1.3.2. can't miniaturize as the phyics at small scale then has trouble ramping up.

3.1.4. data integration and automated analysis

3.1.4.1. software packages need to be inhouse. can't just use it when at the foundry

3.1.4.2. data mining / analysis folks need to talk directly with experimentally that generate the data

3.1.4.3. need proper controls and standardized protocols to prevent going down unproductive 'paths'

3.1.4.4. looking at 10% improvements in genetics is tough with minimal variation. Hhard. very hard!

3.1.5. Tools like the trans-proteomic pipeline did part of the task of normalizing data via standards.

3.1.6. need robust statistical analysis

3.1.7. Systems of analysis that are robust to missing data from compensatory pathways.

3.2. Are there new assays that need to be developed?

3.2.1. careful flux analysis

3.2.2. collecting big datasets is really not that helpful unless know what to do with in before doing in!

3.2.2.1. focussed targetted questioning is much better than big datasets

3.2.2.2. need plan for utilizing it that is productive

3.2.3. Informative data is the key. More uninformative data (think genome wide association studies) does not help. Maybe tools to find the most useful data?

3.2.4. Being able to take a snap shot of all similar enzyme activities at one time, thus determining the presence of many compensatory paths at the same time might be interesting.

3.2.5. Line up assays tools that allow us to come in with good confidence that we will be successful when make a measurement and that it will reduce our time to market.

3.3. What is an appropriate balance of high-throughput low-content data vs. slower, high-content data?

3.3.1. high throughput is weekout step

3.3.1.1. what unique role would the foundry play?

3.3.1.2. translatable screening!

3.3.2. tool that rank how informative a dataset is

3.3.3. most data uninformative. tool that finds informative data

3.3.3.1. no intuitive how you predict what type of data will help you improve the process

3.3.3.2. got to find a high-throughput assay that is useful

3.3.3.3. what are next generation detection methodologies that will enable informative data collection

3.3.3.4. would aptamers be helpful? can they broadly be developed?

3.3.3.5. equipment for this testing? what is most useful function for foundry in this testing phase?

3.3.3.6. more than willing to travel to gather excellent datasets that produces informative results

3.3.3.7. technology for broad high-throughput testing

3.3.3.8. at end of day, everyone needs high tighters

3.3.3.9. activics (sp?) approach. monitor several pathways at the same time. POWERFUL!

3.3.3.10. LCMS and GCMS capability are everywhere.

3.3.3.11. MS is SLOW-- extremey low throughput

3.3.3.12. 25 plates a week is LOW throughput

3.3.3.13. 60 plates a day is approaching HIGH throughput

3.3.3.14. build different classes of high-throughput assays. When get client, decide what class of assay(s) is germane

3.3.3.15. could mass tag everything; increase throughput

3.3.3.16. not so much money (in industry); time is more important. need to satisfy investors. so yes, wait to get clients until you have assays working; otherwise they will be dissapointed and won't come back or be satisfied

3.3.4. make libraries of classes of enzymes to help assign functions to proteins of truly unknown function

4. 2:45 PM - LEARN: MACHINE LEARNING AND STATISTICAL METHODS FOR IMPROVING DESIGN, BUILD, TEST, PROCESS INTEGRATION, AND SCALING - Facilitated by Katy Christiansen

4.1. What are the biggest barriers for learning from successful (and failed) biological process design?

4.1.1. databases don't all talk to eachother

4.1.2. is all of your data in a database?

4.1.3. are your databases standardized

4.1.3.1. metrics around quality

4.1.3.2. don't put in if of questionable quality

4.1.3.3. how to judge?

4.1.3.4. process controls: are they in spec?

4.1.3.5. internal standards

4.1.3.6. instrument calibration

4.1.3.7. do you believe a 10% variation

4.1.3.8. how do you normalize for day to day variation

4.1.3.9. needs to be objective quality control

4.1.3.10. this level of quality control is very challenging

4.1.3.11. data when you begin is VERY easy

4.1.3.12. get close to 80% of theoretical yield. then need higher precision than when you began. industry deals with this on a daily basis. academia is likely not aware of this at all

4.1.3.13. what screens will give you accuracy below 2%?

4.1.3.14. all depends on vision? discovery and early stage, then don't need high precision. if bring 20 year old strains and we will clean and get improvement -- then need high precision

4.1.3.15. data entropy.....a real concept. can pull back together if automated systems. collect all data is helpful

4.1.3.16. a lot of mythology about big data. heterogenious noisy and mixed up. control control control

4.1.4. analytical methods with accuracy and precision to measure small percentage changes

4.1.4.1. think high energy physics analogy.

4.1.5. measure a larger range of analytes accurately

4.1.6. should labs play in 79-80% theoretical yield 'space'?

4.1.6.1. likely company specific; might be more efficient in industry

4.1.6.2. if new, maybe; if worked to improve from 0-80, then should stay in company

4.2. What kinds of information sharing would be helpful and acceptable?

4.2.1. how much information should be walled off?

4.2.2. comes down to IP agreements and from company to company

4.2.2.1. chicken and egg problem?

4.2.3. what would be helpful for foundry to share?

4.2.3.1. all raw data would be bad!

4.2.3.2. !!!want to learn enough so that are designs get better/more efficient!!!

4.2.3.3. process data integrated into software package?

4.2.3.4. data in standard format is requisite

4.2.3.5. is data going to be processed?

4.2.3.6. who is customer in this scenario?

4.2.3.6.1. design is the customer

4.2.3.7. don't they just care about titer?

4.2.3.8. just deliver the strain to the customer?

4.2.3.9. in house use may be all that is required

4.2.3.10. if can't use all data in foundry, then we can really learn and become more efficient

4.2.3.11. why not learn from all/other designs?

4.2.3.12. toogle and anonymize so don't vioate proprietary use. Trextron model works like this

4.2.3.13. PAY MORE IF CAN'T USE YOUR DATA TO LEARN

4.2.3.14. add the potential to add their own information. let the database grow from other centers/research entities/companies

4.2.3.15. how to incentivize peopls to dump data there

4.2.3.15.1. data as currency

4.2.3.16. worry about quality of outside data

4.2.3.17. other incentives to share: good PR, currency could be data; higher prioritization to experiments or assays or ???

4.2.3.18. industry cares about the bottom line. may not be true for startups

4.2.3.19. incentive for small companyies?

4.2.3.20. learn from semiconductor industry. this MUst have been worked out

4.2.3.21. doesnt' work as just be an aggregator of data. how does that really help? does it really advance?

4.2.3.22. this foundry generates quality sources of data

4.2.3.23. where is the line between basic science and design and IP?

4.2.3.24. what defines IP in this Foundry effort?

4.2.3.25. basic science leads to IP.....protects to be commercialized

4.2.3.26. what should we pantent and what should we not and just give away

4.2.4. data standardiization resurfaces:

4.2.4.1. how do we avoid customericaion.

4.2.4.2. should Foundry be chahrged with standardization

4.2.4.3. what does a std data set look like?

4.2.4.4. can Foundry force standardization of datasets

4.2.4.5. standardization would help most companies, respective of size

4.2.5. can we envision uses of high performance computing

4.2.5.1. usually data limited, not computation limited

4.2.5.2. use maching learning, etc

4.2.5.3. need to learn from data, still a challenge

4.2.5.4. how do you sruvey 100,000 strains? getting the data currently is much harder than processing it. proccessing may be limitig in the future if throughput can be increased

4.2.5.5. softare not that epensive. it is the people that know how to use it that 'up' the costs.....

4.3. How can learnings be transferred across contexts?

4.3.1. problem of gathering datasets in standard formats for creating big datasets

5. 4:00 PM - PROCESS INTEGRATION AND SCALING: BIOPROCESS DEVELOPMENT AND SCALING, INCLUDING FEEDSTOCKS CONSIDERATIONS AND INTEGRATION WITH LEARN - Facilitated by Gregg Beckham / Dave Thompson

5.1. What are the biggest barriers for understanding how process integration and scaling can inform biological design?

5.1.1. maybe not scale every process. Pick one ad address. is there a generic approach for scaling and separating

5.1.2. investigate different spaces (precipitating, volatiles, hydrophillic, hydrophibic). use model molecules for each class

5.1.3. if can speed scaling, then worthh the investment for government/Foundry

5.1.4. design in robustness, feedstock range, etc.

5.1.4.1. start with clean sugars, go to low grade sugars, finish with cellulosics with phenolics

5.2. For a biorefinery needing to process variable feedstocks and different feedstock types, what do you see as the advantages and disadvantages of each approach listed? List other approaches if needed.

5.2.1. Flux analysis and additional genetic modification of the organism to minimize the impact of these aspects of the feedstock variation

5.2.2. Additional process unit operations (separations) to produce slip streams with the desired characteristics

5.2.2.1. companies out their that are working to circumvent problems with crude sugars/ligno cellulosics

5.2.2.2. goes back to host selection and engineering in nontraditional organisms. many would be chosen that are toerant to crude sugars

5.2.2.3. need technoeconomics of this before you decide

5.2.2.4. more important for high value/low cost

5.2.2.5. public perception issue. public demands using something other than sugars.

5.2.2.6. for consumer projects, they'll want to know how they are made. if from corn, public will become more and more concern about it (any row crop, not just corn). There are sources of sugar from wasteproduct. should be on the forefront of that!

5.2.2.7. food versus fuel

5.2.2.8. or food to food, even!

5.2.2.9. how can we be more efficient with the land that we have.

5.2.2.10. conclution: get clean sugars from lignocellulosic

5.2.2.11. or innvent suite of hosts that are tolerant to dirty sugars

5.2.2.12. Again, TEA shold be driving decisions and processes

5.2.2.13. feedstocks tied to separations downstream!

5.2.2.14. alternative hosts? photosynthetic, non traditional, lignin degraders, syngas utilizers, methanotrophsand, and more

5.2.3. Preprocessing/blending the feedstock(s) to minimize the variation prior to conversion

5.2.4. Ability to utilize a broad range of substrates

5.2.5. environmental issues and the source of sugars are important factors

5.2.6. need host organisms that can utilize waste products

5.3. Given physical characteristics of different feedstocks vary widely, do you see this as an important issue to consider early in the development of the process in order to speed the commercialization process? Why?

5.3.1. feedstock variability affects success in scaling

5.3.1.1. should this b e considered as a huge compoent that drives speed to scaling

5.3.1.2. needs to understand cost/benefits with variability of input. live with. engineer out. fix inputs.

5.3.1.3. need to think about feedstocks issues early on to maximize success going forward

5.3.2. should Foundry play around and optimize feedstocks or just pick one or two and 'live' with them

5.3.3. whole host of organisms and enzymes that are needed to break down lignocellulosics. just another task for the foundry

5.3.3.1. leverage work already going on. conferences on this topic all the time. tons of efforts in europe and elsewhere. fundamental right to operate will depend upon feedstock selection (from public point of view(

5.4. For a feedstock-agnostic or robust biorefinery, what do you see as the advantages and disadvantages of each approach?

5.4.1. public perception and "right to operate" will be an important determinant of the biomass

5.5. What do you consider to be the main hurdles between a strain producing low titers of a target molecule and a scaled-up, pilot-ready version for deployment? What costs the most and what takes the most time?

5.5.1. Leaky/toxic material removal. Phage resistance. Minimal evolution. Multiple product application. Synthetic compartmentalization, not of just an enzyme, but a full genetic system and translation process i.e., programmable droplets that can then easily be added to and broken apart to harvest materials via collapse of an emulsion.

5.6. Aerobic vs. anaerobic processing?

5.6.1. TEAs very different

5.6.2. if can get more aerobic hosts, great. anaerobic very challenging. new electon acceptors would be helpful

5.6.3. contamination leads to huge costs

5.6.3.1. how can we engineer out potention for contamination. huge economic impact

R&D DESIGN 10:45 AM: PICK THE TOP 3 BARRIERS

Votes Cast: 15 Abstained: 5

BARRIERS	COMMENTS	MEAN	STD. DEV.
high throughput gene synthesis	**1.** outsource to industry is current model. Expected to stay the same within Foundry **2.** turnaround time is important **3.** one example using 1.8kb cut off to outsourcing versus in house.....time is killer. inhouse might be faster??? **4.** foundry may be able to capitalize on JGI resources. Current consortium using JGI processes **5.** 1.8 kb is a cut off as this is a great sweet spot for outsourcing. It is nearly impossible to to outsource 2000 constructs at 20 - 30 kb in length and get them back within 3-4 weeks **6.** would be helpful to have a thermophile in inventory to work with. How hot? within the realm of not having to cool it. **7.** that said, the capabilities to generate this type of high throughput synthesis of relatively large constructs mentioned in comment 5 is available for companies with a lot of CapEx investment	0.33	0.47
host onboarding	**1.** promoter range, terminator sequence known and verified? scaled? **2.** thermophiles or other hosts that match process and separations **3.** don't spread too thin.....go unique for extreme pH or extreme temp? **4.** what is spec sheet for 'on-boarded organism' **5.** how to deal with "parts" for a variety of hosts **6.** tiered specsheet for what it means to be onboarded. different levels of	0.80	0.40

	onboarding likely the result **7.** effort for onboarding or organisms likely going to be HIGHLY distributed throughout labs **8.** locus of integration **9.** prokaryotes easy; test all promoters for ~$0.5M **10.** rapid methods for parts validation		
design phase- pre-screening- what gets considered	**1.** focus more on regulatory and IP? easy to export products. highly recalcitrant. length of pathway dictates organism. use advanced tools (e.g., flux/balance analysis). toxicity issues **2.** pathway elucidation. IP-free enzymes!!!! find alternates that catalyze same reaction. **3.** different industries focus on different aspects **4.** S&P500 fund analogy **5.** pathways: elucidation, length, enzyme variants, combinatorial testing **6.** toolkits and characterized range of similar enzymes (e.g., P450 spectrum) **7.** need reliable, cheap database of enzyme evolution. completely random and saturated mutagensis screening **8.** just need to go to market. chemical outcompetes bio processing if known pathway, even if 100 steps. bio path no gauranteed or predictable presently **9.** library of P450 mentioned again. think to be a very useful tool!!!	0.27	0.44
Use of GMO algae restricted in certain locations	**1.** optimize whole system response. **2.** genetic manipulation but use endogenous gene set(s) **3.** very constraining and needs different thought processes **4.** could change if regulatory environment changes **5.** To be clear, algae in Hawaii cannot have exogenous DNA. The algae field can and does use engineered organisms	0.07	0.25
Excretion is an important goal for engineered systems		0.27	0.44
approach to life cycle assessment		0.13	0.34
how to deal with GMO issues	designing organisms that relieve regulatory hurdles downstream is HUGE	0.13	0.34

P450's are important targets - a panel of accessible p450's would add high value		0.00	0.00
Within organism gene utilization to line up with regulatory requirements.	not just gene utilization- overcoming downstream regulatory hurdles	0.07	0.25
standardization of design and centralized and accessible location for validated enzymes and parts for a number of organisms		0.60	0.49
TEA LCA	**1.** have to have well defined process for this to contribute **2.** needs a defined process	0.00	0.00
Too much content and not enough capability will not fly with the big companies that are already doing their own programs.		0.07	0.25
how would technology companies integrate?	**1.** co-developing platforms is a potential **2.** one was exited; can't meet pricepoints; need better systems than what we have **3.** lending software expertise and automation engineering **4.** reward: ongoing question. no mandate to bring money back into company via this endeavor. is there much money that could come from licensing of software tools? **5.** alternatively, there is money to be made from it. remove subjectivity from process. Increase efficiency. Worked in oligo manufacturing business. ex-illumina employees highly sought by field. remove human errors, for example	0.20	0.40
Control drives down cost. Innovators are bad at control. We need to automate discovery, development and production in a seamless system.		0.07	0.25
artificial compartmentalization		0.00	0.00

R&D BUILD 11:45: WHAT WOULD YOU BE INTERESTED IN HAVING AN EXTERNAL PARTNER DO?

Votes Cast: 10 Abstained: 4

EXTERNAL PARTNER RESPONSIBILITIES	COMMENTS	MEAN	STD. DEV.
Genetic tool development to enable engineering		0.90	0.30
Engineering of actual strains		0.30	0.46
Optimization of strains for metabolic flux		0.40	0.49
Optimization of strains for scale-up		0.10	0.30
strains with longer periods of high production rate		0.50	0.50

R&D BUILD 11:45: WOULD YOU BE INTERESTED IN NEW OR NON-STANDARD ORGANISMS?

Votes Cast: 10 Abstained: 4

ORGANISIMS	COMMENTS	MEAN	STD. DEV.
New bacteria		0.40	0.49
New yeast		0.30	0.46
Organisms that both degrade biomass and make a product		0.50	0.50
Organisms that only make the product of choice		0.20	0.40
Extremophiles		0.50	0.50
Photosynthetic organisms (Cyanobacteria, Eukaryotic algae)		0.40	0.49
provide differentiating result for user		0.10	0.30

lower cost operationally	0.30	0.46
need anaerobic and aerobic	0.40	0.49
compartmentalization issues inside cell. make the compartmentalization synthetic	0.10	0.30
Novel eukaryotic organisms with known mating types (for genetic exchange post-strain improvement).	0.20	0.40

R&D BUILD 11:45: HIGH THROUGHPUT STRAIN YES/NO

Votes Cast: 11 Abstained: 6

YES/NO	COMMENTS	MEAN	STD. DEV.
Are you interested in high throughput strain construction?	Yes	0.73	0.45
Would new technologies for strain construction be useful?	robust automation for implementation of new genes/operons/contigs; something for rapid integrations with less error rates/issues than cre lox	0.91	0.29

R&D TEST 1:45 PM: PICK THE TOP 3 BARRIERS

Votes Cast: 11 Abstained: 5

BARRIERS	COMMENTS	MEAN	STD. DEV.
Standardization of fermentation data software/testing		0.64	0.48
There is always a big disconnect between the results obtained at small scale (96-well plates) and shake flasks and fermenters.	this is a major hurdle to overcome. There doesn't necessarily need to be a large disconnect here, but you need to put a huge amount of time and effort to bringing the scales in line. small scale has to be representative of changes seen in big	0.82	0.39

	scale		
sooo much data. so underutilized	**1.** open up all proprietary data formatting so data can be more easily utilized **2.** can't miniaturize as the phyics at small scale then has trouble ramping up.	0.27	0.45
data integration and automated analysis		0.55	0.50
Tools like the trans-proteomic pipeline did part of the task of normalizing data via standards.		0.18	0.39
need robust statistical analysis		0.36	0.48
Systems of analysis that are robust to missing data from compensatory pathways.		0.18	0.39

R&D LEARN 2:45 PM: PICK THE TOP 3 BARRIERS

Votes Cast: 2 Abstained: 3

BARRIERS	COMMENTS	MEAN	STD. DEV.
databases don't all talk to eachother		0.00	0.00
is all of your data in a database?		0.50	0.50
are your databases stanndardized	**1.** metrics around quality **2.** don't put in if of questionable quality **3.** how to judge? **4.** process controls: are they in spec? **5.** internal standards **6.** instrument calibration **7.** do you believe a 10% variation **8.** how do you normalize for day to day variation **9.** needs to be objective quality control **10.** this level of quality control is very cahllenging	1.00	0.00

	11. data when you begin is VERY easy **12.** get close to 80% of theoretical yield. then need higher precision than when you began. industry deals with this on a daily basis. academia is likely not aware of this at all **13.** what screens will give you accuracy below 2%? **14.** all depends on vision? discovery and early stage, then don't need high precision. if bring 20 year old strains and we will clean and get improvement -- then need high precision **15.** data entropy.....a real concept. can pull back together if automated systems. collect all data is helpful **16.** a lot of mythology about big data. heterogenious noisy and mixed up. control control control		
analytical methods with accuracy and precision to measure small percentage changes	think high energy physics analogy.	0.50	0.50
measure a larger range of analytes accurately		1.00	0.00
should labs play in 79-80% theoretical yield 'space'?	likely company specific; might be more efficient in industry	0.00	0.00

R&D PI&S 4:00 PM: RANK FEEDSTOCK ATTRIBUTES

Votes Cast: 1 Abstained: 2

BARRIERS	COMMENTS	MEAN	STD. DEV.
Flux analysis and additional genetic modification of the organism to minimize the impact of these aspects of the feedstock variation		7.00	0.00
Additional process unit operations (separations) to produce slip streams with the desired characteristics	**1.** companies out their that are working to circumvent problems with crude sugars/ligno cellulosics **2.** goes back to host selection and	1.00	0.00

	engineering in nontraditional organisms. many would be chosen that are toerant to crude sugars **3.** need technoeconomics of this before you decide **4.** more important for high value/low cost **5.** public perception issue. public demands using something other than sugars. **6.** for consumer projects, they'll want to know how they are made. if from corn, public will become more and more concern about it (any row crop, not just corn). There are sources of sugar from wasteproduct. should be on the forefront of that! **7.** food versus fuel **8.** or food to food, even! **9.** how can we be more efficient with the land that we have. **10.** conclution: get clean sugars from lignocellulosic **11.** or innvent suite of hosts that are tolerant to dirty sugars **12.** Again, TEA shold be driving decisions and processes **13.** feedstocks tied to separations downstream! **14.** alternative hosts? photosynthetic, non traditional, lignin degraders, syngas utilizers, methanotrophsand, and more		
Preprocessing/blending the feedstock(s) to minimize the variation prior to conversion		4.00	0.00
Ability to utilize a broad range of substrates		6.00	0.00
environmental issues and the source of sugars are important factors		5.00	0.00
need host organisms that can utilize waste products		10.00	0.00
feedstock variability affects success in scaling	**1.** should this b e considered as a huge compoent that drives speed to scaling **2.** needs to understand cost/benefits with variability of input. live with. engineer out. fix inputs. **3.** need to think about feedstocks issues early on to maximize success going	4.00	0.00

	forward		
should Foundry play around and optimize feedstocks or just pick one or two and 'live' with them		7.00	0.00
whole host of organisms and enzymes that are needed to break down lignocellulosics. just another task for the foundry		6.00	0.00

R&D PI&S 4:00 PM: PICK TOP 3 BARRIERS

Votes Cast: 2 Abstained: 2

BARRIERS	COMMENTS	MEAN	STD. DEV.
maybe not scale every process. Pick one ad address. is there a generic approach for scaling and separating		0.00	0.00
investigate different spaces (precipitating, volatiles, hydrophillic, hydrophibic). use model molecules for each class		1.00	0.00
if can speed scaling, then worthh the investment for government/Foundry		1.00	0.00
design in robustness, feedstock range, etc.	start with clean sugars, go to low grade sugars, finish with cellulosics with phenolics	1.00	0.00

WRAP-UP / GENERAL DISCUSSION

1. **Overall thoughts from today.**
   - 1.1. strongly a data source rather than a data sink
   - 1.2. algae is both a feedstock and a host. difficult to build a platform that can be highly leveraged
     - *1.2.1. There are lots of microalgae strains but the state of technology for algae makes it even more important to advance leverageable technologies through a foundry type of organization*
   - 1.3. criticality to having mission
   - 1.4. what is organization structure
   - 1.5. Organization structure and culture
   - 1.6. not be too descriptive
   - 1.7. enabling process technologies
   - 1.8. quality of data is critical. learn from other technologies (e.g. SNP validations). Must mention how data or tools validated!
   - 1.9. scientific advisory and/or industry advisory board(s) would operate best with 9 members :-)
   - 1.10. advisory board could be almost completely from industry.
   - 1.11. work out a way to not compete with people in this room would be GOOD
   - 1.12. is competition bad?
     - *1.12.1. won't join up if competing with industry*
     - *1.12.2. may not be an issue*
     - *1.12.3. enable the next generation of industry*
     - *1.12.4. don't want to double dip for same work*
     - *1.12.5. nanofab at stanford uses old equipment. really good replacement for your garage. could enable smaller players*
     - *1.12.6. larger companies not interested in basic tools; smaller companies scrambling for access to basic tools*
   - 1.13. did not hear anything 'bad'? why not?
   - 1.14. IP is more of a challenge than expected at present
   - 1.15. also need to not reproduce work done by academic consortiums that allow access to early technology/charge membership fee
2. **Please leave your name if you would like to review the report.**